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THE COUNTRY DOCTOR ON THE MAINE COAST*

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MOST persons in my profession, which is the teaching of English Literature, cherish a devotion to the ancient Greeks of the fifth century B.C., that golden age of poetry and drama. I share that devotion. My freshmen at Smith College always read with me a play or two of Euripides or of Sophocles, and I take great pleasure in reading to them the *Apology*, the *Crito* and the *Phaedo* of Plato so that they may know at least something about the life, the noble thoughts, and the death of Socrates.

But there is one Greek writer of this great and golden age of Pericles whom I do not share with my freshmen. He is reserved for my own delight, for those hours when one escapes from students either by going to bed with a book or by driving to the Berkshires in one's car, or by locking oneself within one's office and placing a curt sign upon the door. This ancient writer needs no introduction to this audience. You have been familiar with his name from the day you entered medical school. You are bound by his oath, and you doubtless know far more than I know about those books which he left behind him, some perhaps not written by him but all concerned with ancient medicine and all known by his name. I refer, of course, to Hippocrates, and to his books dealing with acute and chronic diseases, with fractures and head wounds, and swollen joints, with epilepsy, called by him "that sacred disease," with fevers, which seem to have been his chief interest, with childbirth and even with the common cold.

My first interest in Hippocrates began years ago in college when I had two passions: one the study of Greek, the other the dream of being a country doctor and ministering to the sick. The first in my youth was quite safe and sane; the second I kept discreetly to myself, for in those days, at least in rural Maine, the idea of a woman studying medicine was a completely insane notion. Needless to say, the second dream never came true. I must wait for another world for its realization, but the first pleasure — that of the study of Greek — has never left me, although my early knowledge of that language has become tarnished and wasted with the years. I fortunately, however, possess the *Loeb Classical Library*, which gives me Hippocrates in four volumes, and I often delve into these, since the English translation is happily on each opposite page.

Hippocrates, as you know, came from the Island of Cos in the Aegean Sea. He must, therefore, have been reared among island people, fishermen and sailors, and I have a feeling that rural doctoring must have been interesting to him even after he went to Athens and became the great physician of his age and the teacher of young medical students as well. At all events among his many treatises, case histories and medical aphorisms, he has a good deal to say about the dignity of the profession in general, about the behavior of doctors toward their patients and about certain simple remedies that have always reminded me of the ones I grew up with as a child on the coast of Maine. I have chosen a few of these warnings and prescriptions to use as the framework to what I shall try to say about the country doctor as I knew him on the Maine coast many years ago.

Hippocrates says that doctors should always be clean and well dressed and smell pleasantly. The two country doctors, named, respectively, Dr. Rufus Grindle and Dr. Otis Littlefield, whom I knew for many years in the village of Blue Hill, Maine, and one of whom brought me into the world, were, I am sure, as clean as a Saturday night bath by the kitchen stove could make them. They dressed as well, I am sure, as their slender resources allowed, and they surely smelled strongly and, to me, at least, pleasantly, since they always carried about with them the smell of the barn where they cared for their horses and cows, of the old laprobes, which they sat under all winter on their household calls — in other words, of harnesses, manure, hay and grain bins.

Hippocrates says in several places that nature is the best doctor and that most sick people recover anyway of most ailments simply by the wise provi-

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sion of the gods who have made us as we are. We surely believed that doctrine on the Maine Coast in my childhood. We depended on the body to right itself by itself, and the remedies we used to help it along were, for the most part, those of nature herself, gathered from her own fields and pastures. A great-aunt of mine was a faithful herb gatherer, bringing home all summer apronfuls of pennyroyal, wintergreen, wormwood, camomile, thoroughwort and mullein, and, whether we were ill or not, we drank huge quantities of the liquids brewed from these just as a precautionary measure against any diseases that might be lurking about. In addition, our home like most others kept on hand a bottle of Jamaica ginger, one of castor oil, one of Johnson's horse liniment, some spirits of niter, some essence of peppermint, some paregoric, and plenty of homemade cough syrup made by boiling molasses and vinegar together. There were plenty of onions for poultices, and the salt pork barrel in the cellar could always provide a generous slice, which, sprinkled with pepper and bound about a sore throat, was almost certain to cure it.

In fact, when I was a child, to call the doctor in was a momentous family decision. In the first place, it meant that the case was too serious to depend any longer on nature, assisted only by household remedies. In the second place, it meant that you were financially prepared for an unusual expenditure of money. Of course, if you were at all able, you went to the doctor's office at his house, a much confused room in which there was everything under the sun from an old couch, on which you might be asked to stretch yourself, to a checkerboard, upon which, after your professional interview was over, the doctor might ask you to try a game with him. Such an office visit cost you only fifty cents whereas a call at one's home cost a dollar. And in the third place, to call the doctor in meant that you were pleasantly prepared to receive great importance and concern in the eyes of your neighbors. When I was a child, the saying, "She's Had the Doctor," was one to conjure with. A child who had the doctor for anything short of a broken leg or a bad case of measles was raised to indescribable importance among his playmates, and a country woman who had the doctor for anything but the advent of a baby was assumed to be at the door of death.

When the doctor was once summoned, which meant a journey to his house in pre-telephone days or, if you lived far in the country, a message carried by a worried neighbor who was driving to the village, the whole family prepared for him in hushed silence. Clean sheets were put on the bed of the patient, who himself was in a dither of excitement and importance, the house was tidied up, clean towels were placed by the kitchen sink, a kettle of water was kept boiling on the stove, and the best sauce dishes were laid out to receive the doctor's pills and powders. Meanwhile all the unoccupied members of the family found some excuse to call upon the neighbors to give the ominous word that the doctor had actually been called.

The doctor always took his time in coming. He had, of course, to get his black bag ready, to harness his horse and perhaps to drive several miles over all manner of roads. I remember the untold excitement that prevailed when at last he drove into our yard, hitched his horse to the barn door, or left him standing unhitched, and came through the side door into the kitchen. We all stood about in awed silence. My mother in a clean white apron stood ready to execute his commands and to conduct him to the sickroom. He always rubbed his hands over the kitchen stove if it were winter, then washed them at the kitchen sink, and dried them on the best towel laid out for him. Then he was likely, before he was taken to the patient, to have a word with each of us, to chat pleasantly about the weather or town affairs, and even, in spite of his Hippocratic oath, to gossip a bit about his other patients, who were, of course, known to us.

My mother always accompanied him to the sickroom, carrying a tumbler of fresh water, a towel and a spoon, by which he could look down his patient's throat. The first thing, as I remember it, that the doctor always said, after he had shaken hands cheerfully with the patient and inquired minutely about all his symptoms, was a remark I rarely, if ever, hear today: "Let's see your tongue." After the tell-tale member had been scrutinized, and the pulse and temperature taken, the doctor began thumping and prodding most of one's anatomy, looking for rashes, feeling one's feet.

This done he made a pleasant social visit with his patient, to whom he was careful to say nothing alarming about his condition. He talked of village affairs and coming events, ball games and horse races, or anything else that might be diverting. It was characteristic and, I may say, wise of our country doctors, if the patient happened to be the head of the family, to say nothing of politics. As a matter of fact, although Dr. Rufus Grindle was a staunch Republican, Dr. Otis Littlefield was an equally staunch Democrat in an overwhelmingly Republican community. Most heads of families who employed him deplored his politics, but welcomed his skilful ministrations and admired him in spite of his unfortunate political principles, which he was careful never to bring into a Republican sickroom lest mounting fever should result. Dr. Rufus Grindle was equally careful not to argue on politics with any rare patient who was a Democrat.

When the doctor emerged at last from the sickroom, my mother led him to the parlor, where behind closed doors they conferred together. Both our doctors, and I am sure all others on the Maine coast in those days, had high regard for the common sense, skill and even medical knowledge of country mothers and always treated them with

great respect. Neither of our doctors really approved of my mother's homeopathic case, which contained little bottles of pleasant pills marked "Aconite," "Belladonna" and "Nux Vomica," but she used it all the same. The doctors did approve however, of various other treatments; in fact, my mother, like many other New England women, was known far and wide for her knowledge of how to treat the sick.

For earache she used a large raisin, which she heated on a hatpin over a kerosene lamp and placed in the ear, followed by a bit of cotton. This operated, I presume, on the principle of a fireless cooker, and I remember many an earache soothed by it. The great Galen, physician to the Roman Emperor, Marcus Aurelius, is said to have prescribed for toothache and swellings of the face tiny frogs boiled until they were steaming hot and, like the raisins, capable of retaining heat. For chest colds my mother first rubbed us lavishly with hot grease (goose or duck grease, if it were at hand) and then put on a stinging plaster made of mustard and white flour. Even Hippocrates, who depended a great deal on sweating, did not regard it more highly than my mother and our country doctors. We used to sit for half an hour before bedtime with our feet in a pail of hot mustard water. Then we were put to bed surrounded by hot soapstones, and in the morning we were damp but cured.

Hippocrates has a great deal to say about gruel. He believed it should be made of barley meal, either thick for nourishment or thin for sweats. Our doctors agreed with him, and so did my mother. "Give her some gruel, all she wants," our doctors used to say. I never hear a doctor use this old word nowadays, nor can I find a recipe for gruel in my modern cookbooks, but it used to be delicious in a yellow bowl and always gave one that pleasing sense of being ill and, therefore, important.

When all these prescriptions had been suggested and the doctor had left his medicines, pink pills in one saucer, some neatly folded white powders in another, he prepared to take his departure, although he never seemed to be in the least of a hurry. While he was strapping up his black bag, my mother produced his dollar, for most families preferred to pay him on the spot. He always stuffed the bill into a pocket as though he were not much concerned with it.

My mother and I a few years ago had an amusing time reckoning the doctor's bills of our family of six children over a period of sixteen years, from 1886 to 1902. According to our good memories assisted by some accounts of hers, they all amounted to the sum of $105. This amount had paid for the advent of six babies, six cases of measles, one serious case of rheumatic fever, one very bad cut with an axe, six vaccinations for smallpox and a supply of medicine for the sixteen years. I came into the world at a cost of $8.00 — $5.00 for my birth and three follow-up visits to my mother at $1.00 each. My brothers and sisters cost the same, which meant an outlay of $48 to start the Chase family. The measles, since we all had them at once, cost $4.00 for four visits, and the axe injury set us back $7.00; the vaccinations performed in the doctor's office cost 50 cents each, and the rheumatic fever, which gave us enormous social prestige since the doctor came every day for a month, cost $31. The rest of the $105 paid for all the medicine, not of our own making. I do not know the cost of a brother and sister born after 1902, but I do not assume that it was much higher. I may add that all eight of us flourish today in spite of our humble beginnings and modest cash price!

Hippocrates and the great Galen after him, in ages rife with superstition and quackery, did not like superstitions, and yet they say that sometimes a belief in them proves helpful to the patient either in curing disease or in warding it off. Our doctors did not like them either, though they laughingly tolerated them, but yet we flourished on them. We wore each year a camphor bag all winter on a string around our necks; in the spring we were fed a tablespoonful of sulfur and molasses according to the mystic formula of three days and skip three; in the summer we were solemnly warned, and as solemnly believed, that the eating of chokecherries followed within three hours by a glass of milk meant certain death; and we just as solemnly believed that a horse chestnut, carried in one's pocket, would ward off rheumatism and any number of other disasters. A black cotton stocking, worn for at least a week without washing, was believed to cure a sore throat, if it were bound around one's neck at bedtime with the heel against the Adam's apple. I have gone to bed many times with one around mine.

Hippocrates says that of all professions that of medicine is the most distinguished since it aims not only to heal the body but also to calm the mind and spirit. This truth the country doctors of the Maine coast, and elsewhere, of course, understood well. They had never heard of psychiatry, but they knew people, their families, their circumstances, and their worries, and they seemingly had all the time in the world to "talk things over" with their patients. Dr. Rufus Grindle often brought books along, which he thought his patients might enjoy, and, while his old white horse often got tired of waiting and ambled home without him, he might be playing a game of checkers with someone not long for this world. Money never seemed to worry either of our doctors. They cheerfully took their pay, if necessary, in potatoes, lobsters, or a day's labor in their gardens or at their woodpiles. In terms of affection and understanding, as well as of healing, they cared for their patients.

Even now along the outlying districts of the long Maine coastline, they are not extinct. They go hither and yon in their old Fords, chug out to

lonely islands in motorboats, still know their patients as their friends. One of them told me recently that he was still delivering babies on wide-leaved kitchen tables and that he still sometimes resorted to a feather stuck in the patient's nose to induce helpful sneezings. And Dr. Otis Littlefield, who died six years ago at over eighty, full of years and good works, told me a short time before his death, with pardonable pride, that over a practice of fifty years he had brought nearly 1000 babies into the State of Maine and had never lost one of them — or a mother. Quite a record for a country doctor.

Thus is Maine today not bereft of her country doctors. In a State almost wholly rural, except for four or five considerable cities and towns, the doctors are general practitioners rather than specialists, although we boast of some eminent specialists and surgeons also in our hospitals and our cities. We are proud, too, of our small hospitals as well as of our large ones in Portland, Bangor and Lewiston. In my native village of Blue Hill we have a small but beautifully equipped hospital under the able charge of Dr. Raymond Bliss, who for twenty-five years has had an eminent name as a skillful surgeon as well as a general practitioner. Many of our summer residents on the coast, who have been most generous with financial help in building our hospitals, show their confidence in our Maine village doctors and dentists by coddling along their ailing teeth, their appendixes and their gall bladders until the summer comes and they can have their earthly tabernacles depleted, renovated or refurnished by our country dentists and doctors. Our Maine country doctors still have time for their patients' troubles as well as for their bodily ills, and they are still looked up to and honored by us all.

I should like to say a few words in closing — making myself for the moment as spokesman for our small Coast hospitals and our village doctors — in gratitude for a service given here from 34 Bennet Street under the Bingham Foundation. I am told by Maine doctors that the courses given under this Foundation to doctors and technicians is the greatest single help the doctors in Maine have ever had, services that have inestimably benefited the Maine physicians, laboratory technicians and hospitals, and therefore Maine people at large. For this the doctors and the people of the State of Maine are grateful to the State of Massachusetts — states that, until 1820, were both the State of Massachusetts and, even today, in the character of their people, in their coastlines, and in their country villages and their country doctors, are still one and the same.

SERUM CONCENTRATIONS OF PENICILLIN FOLLOWING THE ADMINISTRATION OF CRYSTALLINE PROCAINE PENICILLIN G IN OIL*

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THE use of peanut oil and beeswax suspensions of amorphous calcium penicillin and of the sodium and potassium salts of crystalline penicillin G for delaying its absorption when injected intramuscularly is well known. The recent preparation of the crystalline procaine salt of penicillin G has afforded the opportunity for studying the absorption of a relatively insoluble salt.[1,2] Procaine penicillin is a true salt derived by the stoechiometric combination of procaine hydrochloride and sodium penicillin G. Calculated on the basis of a potency for crystalline sodium penicillin G at 1667 units per milligram, the theoretical potency of crystalline procaine penicillin G would be 1041 units per milligram. The solubility of this salt in water has been found to be about 7000 units per cubic centimeter. This is in marked contrast to the solubility of the sodium and potassium salts of penicillin G. Since procaine hydrochloride and sodium penicillin G combine on a molecule-to-molecule basis, each milligram of procaine penicillin G is equivalent to 0.42 mg. of procaine base. The amount of salt, therefore, possessing an activity of 300,000 units contains about 120 mg. of procaine base.

The activity of procaine penicillin in vitro and its pharmacology in laboratory animals has been defined by Hobby et al.[2] The antibacterial spectrum was shown to be qualitatively similar to that of the water-soluble salt, although quantitative differences were observed in that all the bacteria tested were slightly more sensitive to crystalline sodium penicillin G than to crystalline procaine penicillin G. The latter was shown to be a highly effective agent in controlling experimental pneumococcal and streptococcal infections in mice.

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The purpose of this report is to present pharmacologic data concerning the use in man of crystalline procaine penicillin G suspended in oil.

Materials and Methods

Antibiotic Agents

Crystalline procaine penicillin G suspended in vegetable oil was available in a concentration of 300,000 units per cubic centimeter.* Sesame oil was employed almost uniformly although a small number of observations were made after the injection of preparations suspended in cottonseed oil. All preparations were quite fluid at room temperature.

Method of Administration

The following single intramuscular injections were employed: 1 cc. of procaine penicillin G in oil — 300,000 units per cubic centimeter; and 2 cc. of procaine penicillin G in oil — 300,000 units per cubic centimeter.

A uniform suspension, obtained by vigorous shaking for at least two minutes, was withdrawn from rubber-capped bottles into a dry, sterile 2-cc. to 5-cc. syringe through a dry, sterile 18-gauge needle, which was replaced by a 20-gauge needle for injection. The mixture was injected in the conventional manner, the needle being inserted with an empty, dry, sterile syringe with which it was possible to ascertain that the needle was not in a blood vessel. Administration of the mixture in disposable cartridges containing 1 cc. was performed without difficulty.

Experimental Subjects

Adult male and female human subjects were used who presented no evidence of impaired cardiac, renal or hepatic function. Post-partum female patients and young adults recovering from acute illnesses were in preponderance. In a number of cases the preparations were employed in the treatment of various acute illnesses as the definitive form of therapy.

Determination of Serum Penicillin Concentrations

The serum penicillin concentrations were determined by the method described by Rammelkamp,[3] using a beta-hemolytic streptococcus as the test organism.

Results

Administration of 300,000 Units of Crystalline Procaine Penicillin G in Oil

Fifty-seven subjects received intramuscularly 1 cc. of sesame oil containing 300,000 units of crystalline procaine penicillin G. The serum concentrations of penicillin during the forty-eight hours following administration of this dose are shown in Figure 1. In 19 cases the concentration was determined half an hour after administration and varied from 0.04 to 0.64 units per cubic centimeter of serum. Of the 19 determinations, 16 (84 per cent) were 0.08 units per cubic centimeter or greater, and 9 (47 per cent) were 0.32 units or more. In the subjects in whom serum penicillin concentrations were determined at half an hour and four hours after injection the maximum level occurred uniformly at four hours and varied from 0.08 to 2.5 units per cubic centimeter of serum. The maximum level obtained after a given injection persisted for twelve hours in only 2 cases. Twelve hours after this injection all subjects had demonstrable concentrations of penicillin in the serum, and 34 patients (72 per cent) had levels of at least 0.08 units per cubic centimeter of serum. Assayable amounts of penicillin were present twenty-four hours after administration in 58 of 63 patients (92 per cent). Forty-eight hours after administration 21 subjects (55 per cent) had assayable concentrations of serum penicillin.

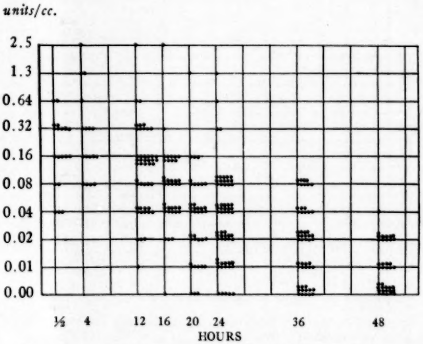

FIGURE 1. *Serum Penicillin Concentrations Following the Administration of 300,000 Units of Crystalline Procaine Penicillin G in 1 cc. of Sesame Oil.*

Administration of 600,000 Units of Crystalline Procaine Penicillin G

Forty-eight subjects received intramuscularly 2 cc. of sesame oil containing 600,000 units of crystalline procaine penicillin G. The serum penicillin concentrations present in these patients during the forty-eight hours following administration are shown in Figure 2. Half an hour after administration the serum contained 0.02 to 1.30 units per cubic centimeter of serum. Sixteen patients (80 per cent) had serum penicillin concentrations of 0.08 units or greater, and 10 patients (50 per cent) concentrations of 0.32 units per cubic centimeter of serum or greater. In all but 2 subjects from whom specimens were so taken the maximum serum con-

*We are indebted to Eli Lilly and Co., Indianapolis, Indiana, Charles Pfizer and Co., Brooklyn, New York, and Schenley Laboratories, Incorporated, New York City, for supplying the crystalline procaine penicillin G in oil employed in these studies.

centration occurred four hours after administration. The penicillin concentration in 1 patient was less than and in another was the same half an hour after injection as that at the four-hour interval. The maximum serum concentration obtained with this dosage varied from 0.08 to 2.5 units per cubic centimeter of serum. The maximum level that occurred in a given subject during the first four hours following injection was present twelve hours after the administration in 12 of 31 cases. The serum concentrations of penicillin twelve hours after injection of this dose varied from 0.04 to 1.30 units per cubic centimeter of serum. Twenty-four hours after injection a concentration of 0.02 units or more was maintained in all cases. Forty-one patients (85 per cent) showed 0.08 units, and 15 patients (31 per cent) maintained 0.32 units per cubic centimeter. Forty-eight hours

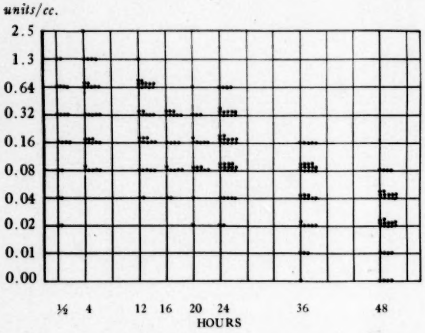

FIGURE 2. *Serum Penicillin Concentrations Following the Administration of 600,000 Units of Crystalline Procaine Penicillin G in 2 cc. of Sesame Oil.*

after administration 32 patients (89 per cent) had assayable serum penicillin concentrations, 28 patients (78 per cent) 0.02 units per cubic centimeter or more, and 4 patients (11 per cent) 0.08 units per centimeter or greater.

Local Reactions

Administration of this material was easily performed in the conventional manner, provided the suspension was thoroughly and vigorously shaken prior to withdrawal from the bottle. Delay in carrying out the injection after withdrawal of the preparation into a syringe resulted in early separation of the suspension and clogging of the injecting needle. There was an almost complete absence of pain at the site of injection, and subjects who had the opportunity to compare the local reaction with peanut oil and beeswax mixtures reacted uniformly in favor of the former. In only 1 of the group of 111 subjects who received well over three hundred injections was a persistent nodule palpable at the site of administration, probably owing to administration of the mixture subcutaneously instead of intramuscularly. No allergic reactions were noted.

Discussion

The serum penicillin concentrations following the injection of 300,000 and 600,000 units of procaine

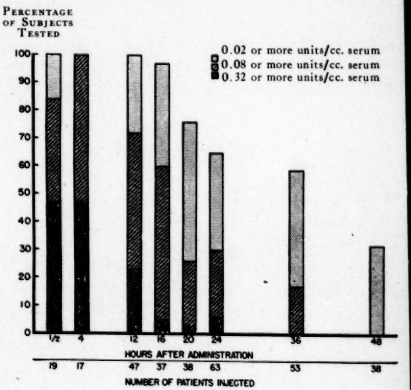

FIGURE 3. *Incidence of Given Serum Penicillin Concentrations Following the Administration of 300,000 Units of Crystalline Procaine Penicillin G in 1 cc. of Sesame Oil.*

penicillin are summarized in Figures 3 and 4. A comparison of the concentrations obtained in this

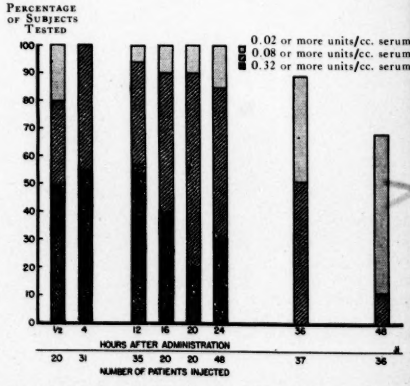

FIGURE 4. *Incidence of Given Serum Penicillin Concentrations Following the Administration of 600,000 Units of Crystalline Procaine Penicillin G in 2 cc. of Sesame Oil.*

laboratory with procaine penicillin G in sesame oil and crystalline sodium penicillin G in peanut oil and

beeswax is made in Table 1.[4] In contrast to the peak levels obtained after the injection of peanut oil and beeswax mixtures, there is a distinct tendency for the concentrations of penicillin to rise more slowly after the administration of procaine penicillin G. The four-hour levels were higher than those obtained half an hour after administration. The maximum serum penicillin concentrations obtained after the administration of procaine penicillin G are distinctly lower than those that follow the administration of the same dose of peanut oil and beeswax mixtures of crystalline sodium or potassium penicillin G.

TABLE 1. *A Comparison of the Serum Penicillin Concentrations Following the Administration of Crystalline Sodium Penicillin G in Peanut Oil and Beeswax (POB) and Crystalline Procaine Penicillin G in Oil (PP).*

DOSE	NO. OF PATIENTS		INTERVAL AFTER ADMINISTRATION	SERUM PENICILLIN CONCENTRATIONS			
	PP	POB		PP	POB	PP	POB
units			*hr.*	*0.08 units/cc. or over*		*demonstrable*	
600,000	35	30	12	94	90	100	100
	48	31	24	85	52	100	84
	37		36	51		97	
	36		48	11		89	
300,000	47	30	12	72	70	100	93
	63	20	24	30	10	92	70
	53		36	17		74	
	38		48	0		55	

Thus, the maximum concentrations obtained after the administration of 1 cc. of peanut oil and beeswax containing 300,000 units of crystalline sodium penicillin G varied from 0.08 to 5.0 units per cubic centimeter of serum as compared with concentrations varying from 0.04 to 0.64 unit after the administration of a similar dosage of crystalline procaine penicillin G in sesame oil.. Even more striking is the range of maximum penicillin concentration following the administration of 600,000 units. With the peanut oil and beeswax mixtures the concentration varied from 0.63 to 20 units per cubic centimeter of serum, whereas a concentration of 0.08 to 2.5 units followed the injection of the same amount of procaine penicillin G. There is a tendency, particularly with a dosage of 600,000 units, for the serum penicillin concentrations to be more uniform during the first twenty-four hours following injection of procaine penicillin G than sodium penicillin G in peanut oil and beeswax. It appears reasonable to assume that the difference in solubility of these two salts of penicillin is at least a major factor in producing this characteristic difference. The influence of solubility as a limiting factor may be further manifest in the comparison of the serum penicillin concentrations obtained with a dosage of 300,000 and 600,000 units. Whereas a dosage of 600,000 units of crystalline sodium penicillin G in peanut oil and beeswax produces a considerable increase in the magnitude of the serum penicillin concentrations during the first four hours after injection, as well as an increased incidence of an effective serum penicillin concentration during the twenty-four hours following administration,[4] the result of increased dosage of crystalline procaine penicillin G is largely one of prolongation of an effective concentration rather than an increase in the magnitude of the level during the four hours following administration. The superiority of procaine penicillin G in oil over crystalline sodium penicillin G in peanut oil and beeswax for maintaining an effective serum penicillin concentration for a period of twenty-four hours after administration is evident from the data presented in Table 1. The effective concentration varies with the infecting bacteria and character of the infectious process present. Thus, while the penicillin concentrations required for the treatment of most of the infections caused by the gonococcus, alpha-hemolytic and beta-hemolytic streptococcus and the pneumococcus fall within the ranges obtained in this study, higher penicillin concentrations than can be obtained with this preparation may be necessary for the treatment of overwhelming infections, bacterial endocarditis, chronic osteomyelitis and infections due to organisms of high penicillin resistance, such as certain staphylococci. It is conceivable that under some circumstances the higher penicillin concentrations that result intermittently from the administration of crystalline sodium in penicillin G in peanut oil and beeswax mixture might make this preparation more effective than procaine penicillin, with which an effective level was not obtained even intermittently.

Another advantage of procaine penicillin G in oil for prolonging therapeutic blood levels of penicillin over peanut oil and beeswax preparations is the elimination of beeswax, which has been cited as a cause of a number of unfavorable local reactions. The local reactions following the administration of procaine penicillin were significantly less than those that followed the use of peanut oil and beeswax.

Allergic reactions after the administration of penicillin in peanut oil and beeswax are higher than those following the use of aqueous penicillin. The incidence of such reactions after administration of procaine penicillin in oil remains to be determined. The activity of procaine penicillin G presumably depends

upon the dissociation of the molecule into its respective members, and patients who are allergic to penicillin or to procaine will probably be sensitive to this preparation. The toxicity of procaine itself is of interest in this regard inasmuch as some persons are hypersensitive to this agent. Furthermore, the toxicity of procaine penicillin G is determined by the amount of procaine base present in the compound.[2] This conforms to previous studies with soluble salts of penicillin in which it was shown that the toxicity of various salts was determined by the cation present.[5] Three hundred thousand units of procaine penicillin G contains approximately 120 mg. of procaine base. Toxicity to procaine is dependent upon its rate of absorption and its concentration.[6] Inasmuch as the absorption of procaine penicillin into the circulation is so slow, it is unlikely that appreciable amounts of procaine would be present after the administration of therapeutic doses of procaine penicillin G. An intradermal sensitivity test with 1 per cent procaine solution should, however, be performed when suspicion of procaine allergy exists.

Summary

Administration of 300,000 units of crystalline procaine penicillin G in sesame oil produced demonstrable serum penicillin concentrations at twelve hours after administration in all and at twenty-four hours after injection in 92 per cent of subjects studied.

Administration of 600,000 units of this material produced demonstrable serum penicillin concentrations twenty-four hours after injection in all and at forty-eight hours after injection in 89 per cent of subjects studied.

The maximum serum penicillin concentrations obtained with procaine penicillin G in oil were distinctly lower than those following a similar dose of sodium penicillin G in peanut oil and beeswax. The concentrations following administration of the former preparation, particularly with a dose of 600,000 units, showed considerably more uniformity throughout the twenty-four hours following injection.

A comparison of the serum penicillin concentrations obtained after a dose of 300,000 and 600,000 units of procaine penicillin G revealed the most characteristic difference to be a prolongation of a given effective penicillin level rather than an increase in the magnitude of the penicillin concentration during the early period after administration.

Crystalline procaine penicillin G in oil was superior to crystalline sodium penicillin G in peanut oil and beeswax for maintaining an effective serum penicillin concentration for twenty-four hours after injection.

We are indebted to Miss Doris McCarthy for technical assistance.

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PAROXYSMAL HYPERTENSION IN SPINAL-CORD INJURIES*

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MEMPHIS, TENNESSEE

THE purpose of this paper is to report on the clinical significance of a little known, but constantly occurring, phenomenon in high spinal-cord lesions. Mass sympathetic discharge, occurring either in conjunction with "mass reflex" or alone in response to various stimuli, has been noted for many years and was first clinically recorded in the classic papers of Head and Riddoch.[1] Since sweating is the most obvious manifestation of this activity, the mass sympathetic discharge has usually been incompletely designated and has received much attention as "spinal reflex sweating."[2] That the vasomotor component and in particular the severe hypertension may well be the most important part of the syndrome from the standpoint of managing the patient is pointed out below.

The trigger mechanisms that set off the general sympathetic response may be summarized briefly in the words of Head,[1] the first to describe it: "There is scarcely a stimulus, cutaneous, proprioceptive or visceral, that may not be followed by an outburst of sweating appropriate to the lesion in each case." Distention of the bladder, and sometimes of the rectum, has been universally the most common cause in the experience of all.[1–3] The syndrome is manifested by excessive sweating, flushing of the face, congestion of the nasal passages, pilomotor erection, sometimes shivering and a feeling of dullness in the head, which may progress to a severe, throbbing, bitemporal, occipital or frontal headache. Blurring of vision is not uncommon. Objectively the pulse may become slow, irregular and more forceful. The blood pressure climbs almost immediately to precipitous heights, and, if the stimulus is continued, convulsions and loss of consciousness may occur. These changes are quickly reversible when the offending stimulus is removed. Details of the sweating have been adequately described elsewhere.[2] This discussion is confined to the description of accompanying hypertension, which we believe to have been neglected as a field of study. Recent American reviews of the treatment of various stages of paraplegia, or observations of the related sympathetic phenomena, do not mention its occurrence.[3–8] Physicians who have spent much time with paraplegic patients have noted, however, that fluctuations of blood pressure are not uncommon although they have observed no particular pattern to these variations. It appears from our studies that these wide variations in blood pressure are an integral part of a sympathetic response to various stimuli, principally vesicular and rectal in origin. This response has been described as being a component of the mass spinal reflex,[2] a release phenomenon induced by any afferent stimulus acting on the distal portion of the cord, the efferent path being through the thoracolumbar outflow of the autonomic system.

While our work was under way, Whitteridge and Guttmann,[9] who had previously made independent observations along the same lines, published a summary of their studies indicating a profound redistribution of blood flow. This might have been suspected from clinical observations. These authors noted greater blood-pressure changes when the cord lesion was above the level of the sixth dorsal segment. This fact they attributed to an inability of the organism to compensate by selective redistribution of blood flow when the large splanchnic bed was cut off from control of the vasomotor center. Changes in blood flow of the extremities in response to various nociceptive stimuli occur in normally innervated people.[10] Distention of the viscera in normal people also causes vasoconstriction in the fingers and toes.[11] A brief summary of the work of Whitteridge and Guttmann[9] follows:

> In lesions above the sixth dorsal segment they noted a slight rise in rectal temperature and a greater rise in skin temperature of the neck and ears upon bladder distention. As measured plethysmographically, there was a decrease in volume of fingers and toes. There was an initial sharp decrease in pulse rate followed by a normal rate as bladder pressure was maintained. Pulse volume and temperature increased in the ears; meanwhile, temperature of the lower extremities fell.
>
> In lesions below the sixth dorsal segment they found the same fall in temperature of the lower extremities combined with a profound fall in pulse volume of toes, but the blood flow increased in fingers and the blood pressure rose no more than 30 mm. in contrast to increases of 100 mm. or more in the higher lesions. They concluded that in the lower lesions there were still splanchnic areas under vasomotor center control available for compensatory vasodilatation. Distention of the rectum caused a similar syndrome, but the effects were more transient.

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We have confirmed these observations with the exception of the plethysmographic recordings, which we were unable to do at this hospital. Typical experimental studies at various levels of the spinal-cord injury are discussed below.

Method

The patients were placed in recumbent position, and a tidal drainage apparatus with a cystometric manometer attached to a No. 16 Foley catheter

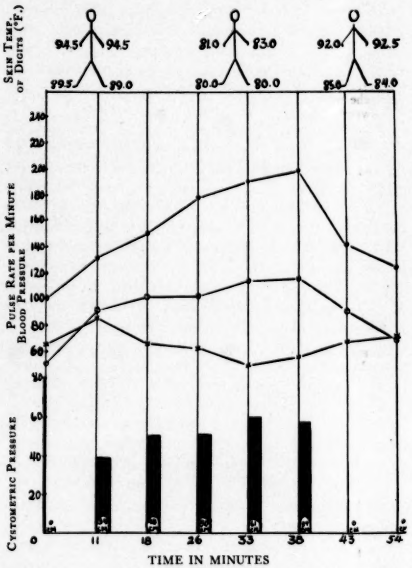
Skin Temp. of Digits (°F.)
94.5 94.5 99.5 89.0
81.0 83.0 80.0 80.0
92.0 92.5 85.0 84.0
Pulse Rate per Minute Blood Pressure
Cystometric Pressure
0 11 18 26 33 38 43 54
TIME IN MINUTES
• = Systolic Blood Pressure
◦ = Diastolic Blood Pressure
x = Pulse Rate/Minute

Figure 1. *Pertinent Data in Case 1.*

previously inserted into the bladder. Skin temperatures were measured directly by a thermocouple (U.M.A. corporation). The subject was placed in a thermostatically controlled room at a constant temperature of 70 to 72°C. for an hour before the procedure, to permit the skin temperature to become stabile. Readings were made from the palmar surfaces of the distal phalanges of several digits of each extremity. Since no essential difference in direction of change occurred among the several digits of any one extremity, the first digit was arbitrarily chosen to be used in the illustrations. Blood pressures were measured indirectly by a cuff and mercury manometer. On certain patients, electrocardiographic and oscillometric records were taken. Observations were made of the blood pressure, pulse rate, gross sweating, pilomotor changes and skin temperatures as the bladder was slowly filled with an irrigating solution ("G solution").[12] Subjective sensations, such as headache, palpitation, rigor and flushing were noted.

The following case reports are illustrative of the type of blood-pressure response that may be experimentally produced by distention of the bladder at the various levels of spinal-cord injury.

Case 1. E. J. C., a 22-year-old man, with traumatic transverse myelitis of 40 months' duration, had a physiologically complete lesion at the level of the fifth cervical segment. He gave a history of spinal sweating, headache and sometimes convulsions of short duration associated principally with urinary-tract infections while he was at another hospital. The blood pressure was not recorded at that time, and no cause for the convulsions was found. The attacks subsided spontaneously when the infections had ended. The blood pressure, cystometric pressure, pulse rate and skin temperatures of the digits are shown in Figure 1. For the last few months the patient has been symptom free.

During this procedure, although no convulsion occurred, the patient stated that the headache and chilliness that appeared with the rise in blood pressure were similar to his difficulties some months previously, which had sometimes caused loss of consciousness and generalized convulsions of a few minutes' duration.

Case 2. H. R., a 22-year-old man, with traumatic myelitis incurred in June, 1945, had a lesion neurologically complete at the level of the seventh dorsal segment and had exhibited

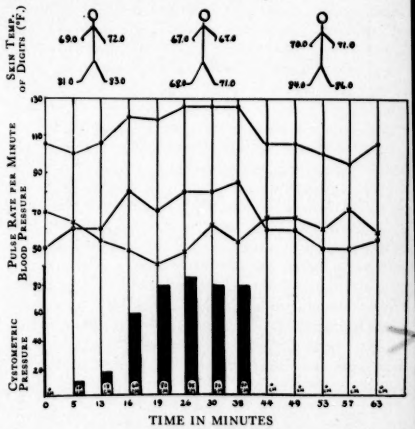
Skin Temp. of Digits (°F.)
69.0 72.0 81.0 93.0
67.0 67.0 68.0 71.0
70.0 71.0 89.0 94.0
Pulse Rate per Minute Blood Pressure
Cystometric Pressure
0 5 13 16 19 24 30 38 44 49 53 57 63
TIME IN MINUTES
• = Systolic Blood Pressure
◦ = Diastolic Blood Pressure
x = Pulse Rate/Minute

Figure 2. *Pertinent Data in Case 2.*

reflex sweating since a few weeks after injury. He had had no cerebral symptoms. Laminectomy done in June, 1947, demonstrated a complete absence of the cord at the level of the seventh dorsal segment. The blood pressure, cystometric pressure, pulse rate and skin temperatures of the digits are shown in Figure 2.

Bladder sensation was completely absent in this patient. The appearance of sweating and pilomotor erection was prompt and severe on both legs but predominantly right sided

n the trunk as high as the level of anesthesia. Dermographia as striking above and below the sensory level, whereas the bladder pressure was high and disappeared promptly when ressure was released.

Case 3. G. L., a 31-year-old man, with incomplete transerse myelitis at the level of the second lumbar segment of 9 months' duration, had developed an automatic bladder ut had never noticed the sympathetic discharges associated vith distended bladder in patients with higher lesions. Thermoregulatory sweating was normal above and below the

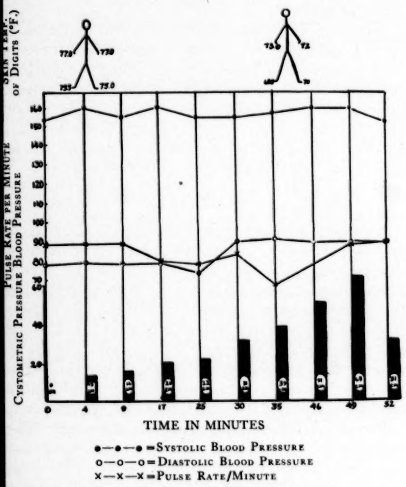
Cystometric Pressure Blood Pressure
Pulse Rate per Minute
Time in Minutes
●—●—● = Systolic Blood Pressure
o—o—o = Diastolic Blood Pressure
×—×—× = Pulse Rate/Minute

Figure 3. *Pertinent Data in Case 3.*

lesion. The blood pressure, cystometric pressure, pulse rate and skin temperatures of the digits are shown in Figure 3.

In this patient, the central pathways of the autonomic system were apparently undamaged. No spinal sweating, pilomotor phenomena or hypertension occurred although, from the skin-temperature changes, it seemed that vasoconstriction was taking place in the extremities, although the systemic arterial pressure remained essentially the same. This case illustrates the effect of bladder distention in a patient with an intact autonomic nervous system.

In the following cases the vasomotor disturbances were of clinical importance in the care of the patient.

Case 4. E. D., a 22-year-old man, with a physiologically incomplete lesion below the level of the fifth cervical segment, since July, 1946, had the following interesting history. A few weeks after traumatic spinal-cord injury, not involving the head, the patient began to have periods of dimness of vision, sometimes severe headache with loss of consciousness and clonic movements of the left upper extremity and facial musculature. In retrospect the patient associated these "attacks" with change of catheter, sudden changes of position and enemas. Complete initial study failed to assign an etiology to this syndrome although electroencephalographic findings suggested "a focus of activity in the right frontotemporal region without seizure discharges." Consultation with the ophthalmologist revealed normal funduscopic findings. "Seizures" were interpreted as epileptiform or its equivalent. There was no other neurologic evidence of intracranial disease. In April, 1947, a suprapubic cystotomy was performed because of postoperative hemorrhage following a litholapaxy. There was a complete and dramatic cessation of these attacks. Repeat electroencephalogram showed no essential change from the previous record.

In retrospect, the possibility that these symptoms were produced by bladder spasm was considered after the patient had been symptom free for 8 months with the suprapubic tube in situ. Consequently we attempted to reproduce these symptoms experimentally by the methods outlined above. The blood pressure promptly rose to 220/115 when a pressure of 90 cm. of water was present in the bladder. The usual autonomic phenomena were noted, and in addition, the pupils became bilaterally dilated, more so on the left. The patient complained of dimness of vision and headache and the facial muscles began to twitch. As the patient began to lose consciousness and became cyanotic, the bladder pressure was released. The patient's symptoms promply disappeared in 3 minutes, and the blood pressure fell to 110/60 — his basal reading.

Case 5. T. B., a 25-year-old man with an incomplete lesion at the level of the fifth cervical segment since September 11, 1946, experienced sudden, throbbing, bitemporal headache with flushing of the face, pilomotor erection, excessive sweating and symptoms of mental confusion and loss of consciousness each time an enema was administered. Other stimuli, such as bladder distention and sudden changes in position from recumbent to upright and turning on the face, invoked the same chain of events innumerable times during the day and night. The symptoms had become more frequent and severe during the last few months. Blood pressures recorded during these attacks consistently ranged as high as 260/140. (This patient had undergone a progressive deterioration of mental outlook because of despair over this severe, additional incapacity.) Tetraethyl ammonium chloride, administered before these procedures, consistently prevented the attacks. This effect was maintained for less than 1 hour, however, and on account of the severity, frequency and persistence of the symptoms, a surgical attack on the sympathetic ganglions is being considered.

Case 6. W. K., a 22-year-old man with incomplete paraplegia below the level of the third dorsal segment, was first

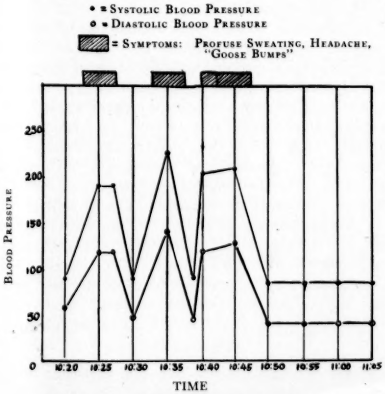
● = Systolic Blood Pressure
o = Diastolic Blood Pressure
= Symptoms: Profuse Sweating, Headache, "Goose Bumps"
Blood Pressure
Time
1000 Mg. of Tetraethyl Ammonium Chloride Given

Figure 4. *Effect of Tetraethyl Ammonium Chloride in Case 6.*

afflicted with excruciating, throbbing, bitemporal headache with the attending evidence of sympathetic discharge while suprapubic cystostomy was being performed. For several days postoperatively the same syndrome occurred every 15 or 20 minutes during the day — somewhat less frequently at night. This was always associated with severe bladder spasm that blocked the urinary outflow at the catheter but subsided spontaneously when flow was re-established. The blood pressure rose as high as 220/140 from a basal pressure of 90/70. Tetraethyl ammonium chloride intramuscularly in a dose of

0.8 to 1.0 gm. dramatically stopped the headache, lowered the blood pressure and abolished the sweating. The patient usually remained symptom free for 4 to 6 hours after injection of the drug, in spite of persistent bladder spasm obstructing the free flow of urine, although spasms were less frequent. After 4 days the bladder spasms became so infrequent that the use of the drug was no longer necessary (Fig. 4).

These blood-pressure recordings were made on the 3rd postoperative night, and the frequency of attacks had gradually increased until one had barely ceased when another occurred.

Clinical Significance of the Hypertensive Component

Since the blood pressures are more labile in lesions above the level of the fifth dorsal segment and since these patients usually have more complications that can provoke the reaction, the hypertension and its concomitant symptoms obviously play a more significant role in this type of case.

The appearance of severe, intermittent headache in high cord lesions should cause the physician to note whether or not this often easily recognizable series of events is in progress. Attention should immediately be directed to the bladder or bowel. The observation has been repeatedly made that blocking of a catheter, acute genitourinary infections and distention of the bowel are attended by hypertension and its concomitants. It should be pointed out that the intracerebral vasomotor change may progress to loss of consciousness and occasionally to the convulsive state, as in Cases 1, 4 and 5. On occasion this may simulate organic brain disease, as in Case 4.

It may easily be seen that the instability of blood pressure in high cord lesions may assume importance in surgical procedures. Paroxysmal hypertension during operation not infrequently taxes the ingenuity of surgeons in control of hemostasis. This is particularly true in resection of hypertrophic bladder neck when the bladder is mechanically distended by hydrostatic pressure. During long operative procedures care should be taken that the bladder does not overdistend. Distention of the bladder sometimes accounts for the hypertension seen toward the end of long plastic and orthopedic procedures in high cord lesions. There is some evidence that a postoperative cerebrovascular accident is provoked by this mechanism.

Treatment

The obvious treatment is removal of the stimulus but this is often impossible, as in Case 4, in which the administration of an enema became an extremely painful process. It is for such patients that we began to search for an agent to block the reflex. Tetraethyl ammonium chloride (Parke–Davis)[13] has admirably filled this need, as indicated in Figure 4. This experience has been duplicated repeatedly in natural and artificially induced attacks. None of the usual sedatives and analgesics had any noticeable effect. In some patients as little as 400 mg. of tetraethyl ammonium chlorid administered intramuscularly, was immediate effective although for a much shorter time than wit larger doses.

Preliminary, and as yet incomplete, studies wit paravertebral procaine blocks indicate that bilatera lumbar sympathetic blocks are insufficient to sto the reflex. Relatively small amounts of procain injected in the lumbar subarachnoid space, however were effective in 2 cases.

In only 1 patient were symptoms sufficiently severe, prolonged or frequent for sympathectomy to be considered. Successful segmental sympathectomy for excessive spinal reflex sweating has been done,[2] but its effect on the paroxysmal hypertensio has not been recorded. We suspect, however, that in these few cases an extensive procedure of the Smithwick type should be considered.

Summary

Attention is called to the phenomenon of paroxysmal hypertension associated with mass sympathetic discharge in high cord lesions. We have confirmed certain aspects of recent studies regarding the accompanying vasomotor changes. The diagnostic and therapeutic importance of this syndrome is emphasized. Tetraethyl ammonium chloride is an effective drug in its symptomatic control. The possibility that an occasional patient may require surgical sympathectomy for relief of symptoms is proposed. A few typical cases are presented. The controversial physiologic interpretations are not discussed. A number of lines of investigation suggest themselves. These include the effect of autonomic drugs and further studies of the hemodynamics.

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PUBLIC HEALTH TODAY AND TOMORROW IN MASSACHUSETTS*

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BOSTON

PUBLIC health is primarily the responsibility of state and local governments. This responsibility, however, must be shared by the medical profession and hospitals if the benefits from recent advances in the medical sciences are to be extended to all the people. For over seventy-five years the Massachusetts Department of Public Health has been serving the people of the Commonwealth in an effort to prevent disease, prolong life and promote optimal health. Almost a hundred years ago Lemuel Shattuck, alarmed at the unusually high death rate among those in the prime of life in the Commonwealth, conducted a sanitary survey. Shocked by the untimely deaths of the inhabitants, he realized that the essentials required for healthful living should be made available to all people. Nineteen years later this survey culminated in the creation of the first state department of health. The Massachusetts Medical Society vigorously supported the creation of the Department and throughout the ensuing years has co-operated in the extension and improvement of public-health services in the Commonwealth.

PUBLIC HEALTH TODAY

The evolutionary development of the Department from the small nucleus of 1869 has been a gradual but constant process. Today, it employs approximately 1,800 people and expends an annual appropriation of approximately $7,250,000. In addition to its other activities, the Department is responsible for the operation of five institutions, eight branch offices and seven laboratories. The federal Government, recognizing its responsibility in the general welfare of the people, annually makes available to Massachusetts approximately $2,500,000 through grant-in-aid programs.

Both the scope and the character of the work of the Department have changed with the passing of years. Primarily concerned with environmental sanitation and the abatement of nuisances, the Department is now engaged in activities pertaining to all aspects of public health. These include the administration of medical care programs, administration of federal grants-in-aid for the construction of hospitals and health centers, the operation of hospitals, supervision and licensing of clinics and hospitals, epidemiology of disease, manufacture and distribution of prophylactic and therapeutic biologic products and processing and fractionation of human blood. The development and promotion of programs dealing with maternal and child health, tuberculosis, venereal diseases, control of cancer and chronic diseases and the research and development of new public-health methods and technics are daily responsibilities of the Department.

Recess Commission on Public Health

A special commission authorized to make a study relative to certain public-health matters was established by Chapter 73 of the Resolves of 1947. This commission was charged not only with the responsibility of considering the licensing of hospitals, convalescent and nursing homes and the co-ordination of local, state and federal activities in the field of public health but also with the laws and policies of the Commonwealth relating to public health. The Commission consisted of Senator Richard H. Lee, Newton, chairman; Representative George W. Dean, Oakham; Representative Joseph D. Rivest, Northampton; Representative Fred C. Harrington, Everett; Dr. Henry D. Chadwick, Waltham, former commissioner of the Massachusetts Department of Public Health; Dr. L. Jackson Smith, commissioner of public health of Springfield; and Professor Curtis M. Hilliard, professor of public health at Simmons College and supervisor of the Board of Health of Wellesley and Weston. The report of this special commission has been published as House Document No. 1766 of the current legislative session.

The Commission organized two technical advisory committees: Dr. Hugh R. Leavell, of Cambridge, professor of public-health practice, Harvard School of Public Health, was appointed chairman of the Committee on Local Health Units, and Dr. Conrad Wesselhoeft, of Boston, clinical professor of infectious disease, Harvard School of Public Health, chairman of the Committee on Preventable Diseases. These committees are continuing their work in anticipation of the continuation of the Special Recess Commission, which submitted a progress report to the legislature on December 3, 1947 (H.1766). The activities of the Commission were directed toward certain major objectives, as follows: the administrative changes in the Department of Public Health; the development of some equitable plan for the establishment of full-time health units throughout the Commonwealth in areas of such population as may be reasonably and economically administered; relocation of the chronic-disease hospital; the licensing and regulation of certain hospitals, sanatoriums and nursing homes by the

*Presented at the annual meeting of the Middlesex South District Medical Society, Cambridge, April 21, 1948.

†Commissioner, Massachusetts Department of Public Health.

Department of Public Health; and consideration of legislation requiring the x-ray examination of schoolteachers and other school employees.

The Commission employed as a consultant Dr. Carl E. Buck, field director of the American Public Health Association, who, with his assistant, Dr. Robert E. Rothermel, contributed valuable aid and consultative advice. The Commission requested its technical advisory committee to make an extensive study of the organization of the Department and to prepare recommendations to the Commission regarding the simplification of the table of organization. As a result of this study, it was recommended by the Commission that assistant commissioners of public health be appointed who would devote their entire time to the administrative duties associated with the five major units into which the Department would be divided. The Commission recommended the consideration of reclassification of both titles and salaries of professional personnel in the field of public health. The Commission became fully cognizant of the fact that the salaries paid professional personnel in Massachusetts do not and cannot assure the people of the Commonwealth the leadership necessary to provide these basic medical services essential to the health of the people. Legislation implementing the recommendations by the Commission and by Dr. Buck was introduced and is now pending in the current legislative session.

Local Health Services

Perhaps the major assignment of the Commission has been the development of an equitable program for the creation of local health units throughout the Commonwealth. The greatest need in public health today in Massachusetts, as well as in the United States, is the development of full-time, adequately staffed local health departments for population groups sufficiently large to enable efficient and economic administration. A preliminary study of legislation pertaining to local health departments and unions of health departments, their duties, responsibilities and services rendered the people has been made in a report submitted. The Technical Committee on Local Health is continuing its work in this field.

Massachusetts may well take pride in the fact that in its health responsibilities, including the provision of tuberculosis hospitals, and in its vital statistics, which reveal a low infant and maternal mortality, absence of smallpox and low typhoid-fever morbidity, it compares very favorably with other sections of the country. However, the Commission has not considered that doing a good job is sufficient. Its report indicated that only the best possible public-health program should continue to evolve in Massachusetts.

Although the Commonwealth has been and is still far ahead of most of the country in such important activities as cancer and tuberculosis control and in environmental sanitation, Massachusetts, as well as the remainder of New England, is far behind the rest of the country in the development of full-time, adequately staffed local health departments for units of sufficient population size to be susceptible of reasonably economic and efficient administration. In the Commonwealth today there are but eleven cities and towns and one county that provide full-time medical health officers not engaged in private practice. These include Boston, Brookline, Cambridge, Fall River, Falmouth, Lowell, Newton, North Adams, Pittsfield, Springfield, Worcester and Barnstable County. There are today in Massachusetts twenty communities of 35,000 population or more not served by full-time medical health officers. Such a condition exists despite the fact that practically all public-health administrators are agreed that the most important public-health need today is the development of adequately staffed full-time health departments. Dr. Carl Buck, of the American Public Health Association, who has recently reviewed the status of local health services in the Commonwealth and who bases his opinion upon the "Evaluation Schedule of Local Health Services," has reported that there are but four health departments in all of Massachusetts that would be judged "good" on the basis of these accepted standards.

Why are the physicians and the people of the Commonwealth so apparently satisfied with the situation as it exists? Simply because Massachusetts rates for preventable causes of death are somewhat better than the average of the country as a whole? Perhaps this is being satisfied rather easily, for in the Commonwealth during the five-year period 1941-1945 inclusive more than 1,500 persons died from the following "preventable causes": diphtheria, 50; measles, 71; whooping cough, 142; syphilis, 1238; typhoid fever, 20; bacterial dysentery, 26; tetanus, 29; and undulant fever, 7. For the same period (1941-1945) over 70,000 deaths from controllable causes occurred as follows: cancer, 37,361; tuberculosis, 7888; lobar pneumonia, 3962; premature births, 4696; accidents, 14,670; meningomeningitis, 279; scarlet fever, 63; maternal deaths, 934; and diarrhea and enteritis (in patients under two years of age) 693. If the knowledge concerning the prevention and control of these diseases that we have at hand could be universally applied throughout the Commonwealth, the saving in lives would be tremendous. Practically all the deaths from preventable causes could have been avoided, and it has been very conservatively estimated that at least a third of all cancer deaths and at least half of all other deaths from controllable causes could have been avoided. Thus, in Massachusetts alone, the saving of over 30,000 lives over a five-year period, or an annual saving of 6000 lives, could have been effected. If a human life is valued at only $5000, this would result in an annual saving to the Com-

monwealth of over $30,000,000. Obviously, the Commonwealth is currently and continuously experiencing an irreparable loss in lives and money. If the essential developments of modern medicine, preventive procedures and programs developed through public health could be made available to all the people these lives would not be lost but would continue to contribute to the assets of the Commonwealth.

In such a program the Government alone cannot succeed. The annual saving of over 6000 lives is a challenge not only to the government but also to the public-health and medical professions. Imagine the sacrifice of 30,000 people every five years in the Commonwealth — a population equivalent to that of the cities and towns of Revere, Belmont, Weymouth and Melrose! It must be borne in mind, however, that these figures represent but a portion of the entire problem. They include no estimate of the amount and extent of sickness or economic loss resulting from cases that do not terminate in death. For example, it is estimated that the annual loss of income of the Commonwealth due to disability from chronic disease is $50,000,000. Is it a wonder, then, that the medical profession and the public are expressing a growing concern about this unnecessary loss of lives and income?

Medical and other professional schools are now training physicians, dentists, nurses and health officers, in an effort to supply the personnel necessary to provide basic health services. Through local resources, voluntary and governmental hospitals and health centers are in the process of construction throughout the Commonwealth. The Department of Public Health is assisting this expansion of physical facilities through the administration of the Survey and Plan for Construction of Hospital and Health Centers in the Commonwealth. By means of this program financial assistance will be offered to some of these projects through a federal grant amounting to $8,000,000, which will extend over five fiscal years beginning on July 1, 1947.

The greatest single need in Massachusetts, however, is the development of local health units, adequately staffed and efficiently serving all the people of the Commonwealth. If full-time health departments are to be established, certain basic essentials must be met:

A sound state-wide program of health education to accomplish as soon as possible a universal understanding of the needs and value of full-time health services.

An active department of health adequately staffed. This is essential for the proper leadership and stimulation of activities throughout the cities and municipalities.

Basic legislation permitting and facilitating the establishment of full-time health departments through unions of towns on a voluntary basis. Approval of the state health agency of such departments would be necessary that no section of the Commonwealth would eventually be without such services. Compulsory formation of such unions may be required if they are not formed voluntarily within a period of five to ten years.

A plan for state and federal subsidy for the maintenance of full-time local health departments.

The training of adequate health officers, public health nurses, sanitarians, nutritionists and medical social workers required for the local health units.

The provision of adequate compensation to qualified public-health personnel. This is an essential, since the recruitment and retention of good personnel depend first and foremost upon good salaries, reasonable tenure of office, opportunities for advancement and reasonable plan of retirement. The last three, of course, may be effectively obtained through a well conducted civil-service system.

Periodic evaluation of services rendered by the community health agencies, preferably through some method of study as that devised in the evaluation schedule of the American Public Health Association. Evaluations of this type have many uses, among them being provision of a base line for future measurement; calling attention to achievements and unmet needs; and furnishing a foundation for future planning.

Of these seven basic essentials necessary to the establishment of full-time local health departments, Massachusetts is lacking in all. Perhaps the best way of meeting the need for the dissemination of health information is through the creation of a state-wide health committee designed to achieve real understanding on the part of the people and the professions of the services and benefits that can be obtained through the extension of adequate local health services.

Although existing legislation permits the establishment of unions of towns for health purposes, such unions have not been successful in the past because of their effervescent nature and failure of financial support from either state or federal appropriations. A plan must be devised for providing various alternate methods for these unions of towns on a county or district basis, which will ensure complete coverage of the Commonwealth within a reasonable time, or the alternative of such a program must be introduced — namely, that such unions be formed after public hearings throughout the Commonwealth have been held by the Department of Public Health.

At present there are but nine states in the entire United States that do not make available state funds to local health departments. Massachusetts is one of these.

The Private Practitioner and the Health Department

Efficient local health departments have always called attention to the need for more adequate medical services. It has been my experience and that of most public-health officials that the more conscious the public becomes of health, the more it utilizes available local health facilities and services. Therefore, the formation of adequately staffed health units throughout the Commonwealth would increase the utilization of services of physicians, dentists and hospitals. Although physicians may as a result of this become more overworked than they are now, such services would consist primarily of preventive measures and the diagnosis and treatment of early illnesses or disabilities rather than the providing of terminal care, which has unfortunately occurred too often. To be sure, prolonged illness and chronic disability will still occur, but effective preventive measures, early diagnosis and prompt and adequate treatment may greatly reduce the incidence.

A private practitioner of medicine has, therefore, a moral obligation to the people to assist in furthering community health programs. At the same time he will contribute to the economic improvement not only of himself but also of his entire community.

Long-Term Illness

Physicians are all concerned with the task of prolonging life and improving the health of patients. Today, with the life expectancy of a newborn infant amounting to almost seventy years, the doctor's responsibility for this life is greater. With advancing age the human body tends to succumb to a host of chronic diseases, such as heart disease, vascular disease, cancer and diabetes, any one of which may be not only prolonged but also often disabling. The medical and public-health professions have made outstanding advances in the control of infectious diseases and the diseases of early life, which must continue, but they must also acquire further knowledge and develop better methods for the early diagnosis of preclinical long-term illnesses. New procedures for the prevention, early diagnosis and amelioration of chronic diseases must be the next major development. Although it may be impossible to prevent heart disease per se, it may be possible not only to reduce its incidence but also to delay the onset of symptoms, postpone the disability period and prolong life for many productive and happy years. By similar methods, the patient with cancer or diabetes may look forward to a longer productive life. This will occur, but the essential prerequisite is that health departments and the medical profession, through co-ordinate action, make available to the people the benefits of new medical knowledge as soon as it is of proved value.

Here again the private practitioner receives a challenge — a challenge not only to promote greater health in the aging population but also to realize and accept the changing goal in his daily practice. Health supervision, through periodic, thorough examination and care of the patient, becomes a physician's increasing responsibility.

Public Health Tomorrow

The education of the patient in healthful living is the dual responsibility of the doctor and the health department. The doctor of tomorrow must not only prescribe well but also inform well. Patients want to know what can be done to improve their health. Today, more than ever before, the public is conscious of its health; people are making greater demands for services upon the Government, hospitals and the medical profession. The future of public health is therefore encouraging. Programs for the maintenance and preservation of health are both improving and increasing in scope. The people, by demanding basic health services, will secure coverage of the nation with adequately staffed local health departments. Improved facilities of hospitals and clinics, the workshops of physicians, will serve more people. The school child will be offered a better opportunity to attain adult life without physical or mental disability, and as an adult, he will be convinced that good health cannot be taken complacently but can be assured only through diligent care under the direction of competent physicians.

Thus, by striving toward the common objective of improving the health of the people the doctor, hospital and health officer may bring to every person the basic essentials, diagnostic, preventive and therapeutic measures that will enable him to enjoy a more productive life and become a greater asset to the community.

MEDICAL PROGRESS

CHEMOTHERAPY OF NEOPLASTIC DISEASE

III. Agents of Clinical Value

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From the large array of substances under laboratory and clinical study, several have been established as useful in the management of patients with inoperable neoplastic disease. These agents are discussed in the order of their value to the clinician, as judged by their unique therapeutic activity and their general clinical effectiveness.

Estrogens

Estrogens are useful in the treatment of carcinoma of the prostate and, to a considerably lesser extent, in carcinoma of the breast. With the fundamental work of Huggins[214] in establishing the role of the steroid hormones in prostatic physiology, the therapeutic value of castration and estrogen therapy in carcinoma of the prostate was rapidly established.[215] Bilateral orchidectomy or estrogen therapy, in 50 to 75 per cent of patients with prostatic carcinoma, will produce rapid and remarkable effects — a decrease in the size of the enlarged prostate, degeneration of many of the neoplastic cells, a diminution in the size of metastases and recalcification of bone lesions, a fall in an elevated serum acid phosphatase level and a relief of pain, urinary-tract obstruction and disability. Hormonal therapy is not curative, however, and the patient ultimately becomes resistant to therapy, but life is often appreciably prolonged.[216, 217] This work has been reviewed by Nathanson.[218]

In the past two years the chief problem in estrogen therapy has been to establish the indications for its use in the proper management of prostatic carcinoma. Colston and Brendler[219] have recommended the use of stilbestrol, 1 to 2 mg. daily, prior to radical prostatectomy. This procedure may possibly convert a localized but moderately advanced inoperable carcinoma into an operable one, and simplify the removal of an operable tumor. Herger and Sauer[220] believe that estrogen therapy is of no prophylactic value in slowly progressing, asymptomatic but inoperable carcinoma of the prostate, and they suggest that its early use may destroy the subsequent estrogen sensitivity of the disease. They have recommended that hormonal therapy be withheld until the disease is extensive or disabling symptoms are present. Deming[221, 222] however, sanctions the use of estrogen therapy in all stages of inoperable prostatic carcinoma. It is generally agreed that since estrogens will produce therapeutic effects equal to castration, their use is to be preferred.[217, 220–222] When immediate relief is necessary, castration is indicated since its therapeutic effects appear within thirty-six hours, whereas estrogens require seven to ten days. Castration is also indicated in patients unable or disinclined to take estrogens, or in those who have relapsed under adequate estrogen therapy. It is not considered likely that castration will help the latter group, but the rare beneficial reports that have appeared seem to justify its trial.[217, 220] Conversely, in cases of castration relapse, estrogen therapy is sometimes effective.[217] There appears to be no good evidence of additive benefits from simultaneous therapy by castration and estrogens.

The estrogen preparations most frequently used are stilbestrol, 1 to 5 mg. daily, and ethinyl estradiol, 0.1 to 0.5 mg. daily. Dean[217] is of the opinion that ethinyl estradiol may be given in larger estrogen equivalent doses than stilbestrol, with less severe gastrointestinal symptoms. Other side effects of therapy are signs of feminization, particularly enlargement and tenderness of the breasts, and a decrease in libido.

The use of estrogens in the palliative treatment of mammary carcinoma is still in the experimental stage, but extensive clinical work is in progress.[223–229] Estrogens do not appear to be active[227, 228] against osseous metastases, which occur chiefly in the younger age groups, and they rarely exert a favorable effect on the disease in this group.[224] Indeed, there is evidence that estrogens sometimes accelerate the course of mammary cancer in young patients.[227] For these reasons, the use of estrogen therapy is entirely confined to postmenopausal patients, and it has been suggested that its use be restricted to women at least five years beyond the menopause.[229] In this group, 30 to 40 per cent of the patients have been found to show some temporarily favorable, but often only slight, response to therapy.[224, 227] This may consist of subjective improvement, regression of local tumors, shrinkage and healing of ulcers, reduction in the size and redness of skin metastases and decrease in the size of lymph-node and lung metastases. The usual

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dosage is 5 to 20 mg. of stilbestrol daily.[229] These large doses may induce gastrointestinal disturbances, with nausea and vomiting, weight loss, diarrhea and uterine bleeding, edema and skin eruptions.

In mammary carcinoma in the male, estrogen therapy has not been tried extensively, but Nathanson[226] has recorded his impression that castration may be therapeutically more effective. Estrogens have been reported to produce tumor regressions in bladder papilloma and subjective improvement in bladder carcinoma.[230]

Nitrogen Mustard

Gilman et al.,[231] early in 1943, first reported, in a confidential military communication, on the clinical use of a nitrogen mustard compound, *tris* (beta-chloroethyl) amine hydrochloride in the treatment of neoplastic disease. Jacobson and his coworkers,[232] shortly afterward, began the clinical use of another nitrogen mustard, methyl-bis (beta-chloroethyl) amine hydrochloride, also known as DEMA or HN2, and this work was extended to two other clinics.[233, 234] Similar work was initiated in England by Wilkinson and Fletcher.[235] Because of military restrictions on the nitrogen mustards, none of the information could be reported until the end of World War II.[114] When these restrictions were lifted in 1946, an official statement was published[236] summarizing the clinical information available at that time, and distribution of the agent for clinical investigation was begun.[237] Since the inception of this study a number of clinical reports have appeared.[238–250]

HN2 must be given intravenously and, therefore, exerts its therapeutic action throughout the body. Recovery from the toxic effects of HN2 is more rapid than that from total body exposure to an equivalent effective dose of x-rays. This makes it possible to control HN2 dosage somewhat more closely than total body irradiation by x-rays or radioactive isotopes.

HN2 therapy has not proved to be a cure in any type of neoplastic disease; in leukemic mice, for example, four to ten times a lethal dose of HN2 in vivo is required to destroy the viability of the leukemic cells, a strain of cells considered to be unusually sensitive to HN2.[28] The rationale of HN2 therapy, therefore, consists in attempting to give the largest amount of HN2 consistent with doing no serious harm to the patient. The amount of HN2 that can be safely given varies considerably in different patients. Important factors in dosage are the patient's general condition, his hematologic status and his immediate prognosis — that is, greater risks can be taken if the immediate prognosis is poor.

The usual course of HN2 therapy consists of the intravenous injection of 0.1 mg. per kilogram of body weight daily for four days, a total of 0.4 mg. per kilogram. This is usually a safe dose, but in some patients with depression of the hematopoietic system, especially that due to bone-marrow involvement with disease, or with very extensive, massive tumors, toxic effects may occur, and the drug should, therefore, be given more cautiously. A course of 0.4 mg. per kilogram of body weight usually produces a moderate leukopenia, which develops gradually within seven to fourteen days, the white-cell count reaching a maximum of 1000 to 3000, followed by a relatively prompt recovery. There may be a mild depression in the platelet count, and usually the hemoglobin level is unaffected. The changes in the peripheral blood are paralleled in the bone marrow.[238] In selected cases the total course of HN2 may be given in two injections of 0.2 mg. per kilogram of body weight or in a single dose of 0.4 mg. per kilogram of body weight. If the usual total course of 0.4 mg. of HN2 does not produce a satisfactory therapeutic result, and the peripheral-blood picture is relatively unchanged or has recovered, within two or three weeks, further HN2 may be given cautiously. In some patients, as a result of experience, it has been found that a total course of 1.0 mg. per kilogram of body weight can be given safely in a three-week period — an amount of HN2 that would prove fatal in other patients.

If an excessive dose of HN2 is given, a characteristic toxicologic picture develops within seven to fourteen days, consisting of severe leukopenia, thrombocytopenia, with petechiae or purpura, a rapidly developing anemia, fever and weakness. The patient may bleed extensively from the nose, gums, kidneys and bowel, or into the skin, and even death may occur. Usually, however, recovery begins within four to ten days. Blood transfusions, as well as penicillin to ward off infections, appear to be the only agents of value in the treatment of this condition.

HN2 has two unpleasant incidental side effects. In many cases it produces thrombosis of the injected vein. This seems to occur more frequently when it is given by the direct syringe method than when injected into the tubing of a freely flowing intravenous infusion. Since the former method is simpler, it is more frequently used. If HN2 escapes from the vein it will produce an extensive local area of erythema, induration and eventually fibrosis. Within one to eight hours after an injection of HN2 most patients feel nauseated, and about 50 per cent vomit.[234] During the course of treatment, the patient may complain of weakness, anorexia and weight loss.

HN2 is not recommended for localized neoplastic disease, which can be treated more effectively with x-rays, with less discomfort to the patient and with longer clinical remissions. The agent has not been in use long enough to permit a definitive statement of its clinical value and the indications for its use.

but the available reports agree about its clinical effects.

HN2 has found its most useful therapeutic role in the treatment of Hodgkin's disease.[232–243, 246, 247, 249] It will induce a consistent clinical improvement in 80 to 90 per cent of treated patients. The most striking effect is detoxification of the patient, with a prompt fall in fever, increase in strength, appetite and weight. Objectively, there may be a decrease in the size of enlarged lymph nodes, spleen and liver, clearing of pulmonary infiltrations, and resorption of ascitic or pleural effusion. Less consistently, there may be relief of bone pain or pruritus, shrinkage of involved, massively infiltrated tissues and recalcification of osseous lesions. A remission may last from two weeks to more than a year, but the average duration is about six weeks. The longer the remission from an adequate single course of therapy, the more favorable the outlook. When the patient begins to relapse, another course of HN2 is usually indicated. Some patients have received more than ten courses of treatment with repeated clinical responses, and with no definite evidence of cumulative damage to the bone marrow. In most cases, however, the disease progresses, and the patient gradually becomes unresponsive to therapy.

HN2 is suggested for the treatment of generalized Hodgkin's disease with systemic symptoms, and for use in patients believed to be "x-ray fast." A significant group of the "x-ray fast" patients may be salvaged for several months or longer by a course of mustard therapy. This does not necessarily mean that the tissue in Hodgkin's disease unresponsive to x-rays can be affected by HN2; it probably does mean that the x-rays were not applied to the areas of active disease, whereas a systemic form of therapy could ferret out these areas. After satisfactory response of an "x-ray fast" patient to HN2 therapy, x-rays may then be used to treat localized disease. There is no evidence that HN2, given early or late in Hodgkin's disease, alters the general course of the disease or prolongs life significantly. It does, however, have an important and unique place in the management of the disease.

HN2 has a definite palliative effect in mycosis fungoides.[244] It will temporarily cause a regression of the skin lesions in patients no longer responding to or unsuitable for x-ray therapy. The duration of remission to a course of treatment is variable, from only several days to six months or longer.

Some patients with lymphosarcoma may respond to HN2 in a truly remarkable fashion, with rapid shrinkage of the enlarged lymph nodes, liver and spleen, and subjective improvement persisting for six months to a year or longer.[231–234, 238–243] Another group with very aggressive disease may also show a marked but unsubstantial therapeutic response, relapsing within one or two weeks. In general, x-ray therapy is more satisfactory for the control of lymphosarcoma. In some patients with extensive but relatively slowly progressive lymphosarcoma, HN2 may give remissions sufficiently long to make it a satisfactory alternative to x-ray therapy.

Consistent clinical remissions can be induced in chronic myelogenous leukemia, with a fall in the white-cell count, a rise in hemoglobin level, a decrease in the size of an enlarged spleen and general improvement in the patient. The remission usually continues for two or three months, and relapse is then fairly rapid. Patients will continue to show some response to treatment until they reach the terminal stage. Wintrobe et al.[243] successfully maintained over many months 2 patients by periodic injections of HN2. There is little evidence that HN2 will prove effective in the treatment of patients unresponsive to adequate x-ray therapy. In fact, in patients with very large spleens, greater relief is obtained from splenic irradiation than from systemic HN2 therapy.

The results of HN2 therapy in chronic lymphatic leukemia have not been consistent. These patients seem to have a greater tendency to develop a toxic reaction to HN2, which should therefore be given cautiously.[234] Occasionally a patient may show a surprisingly good response, with a spontaneous rise in hemoglobin. As Wintrobe[243] points out, however, patients in good condition usually show a good response to HN2, whereas those in poor condition, with generalized lymphadenopathy and anemia, do poorly.

The acute leukemias do not show a satisfactory clinical response to HN2, although a fall in the white-cell count can be produced. Relief of bone pain has been reported.[243]

HN2 will induce a clinical remission in polycythemia vera[17, 246] similar to that produced by radioactive phosphorus. It is too early to draw any conclusions regarding the consistency of this therapeutic effect, or the relative merits or hazards of HN2 therapy compared to other methods of treatment.

In common with other agents, HN2 may cause some relief of pain in multiple myeloma, but there is no substantial evidence that the osseous lesions or the course of the disease is altered.

HN2 has been found to produce transient symptomatic and occasional objective improvement in about 50 to 70 per cent of patients with inoperable carcinoma of the lung.[126, 234, 237] These effects consist of relief of dyspnea and cough, decrease of sputum and hemoptysis and an increase in strength, appetite and weight. The primary tumor and the metastases may show some decrease in size, and absorption of pleural effusions and aeration of atelectatic areas may occur. There is occasionally relief of chest pain, and symptoms from obstruction of the superior vena cava may be markedly alleviated. These therapeutic effects usually last

for from two weeks to two months only, and relapses develop rapidly. Patients with anaplastic carcinoma of the lung show a very dramatic symptomatic improvement, but they relapse quickly. Subsequent courses of treatment are usually not so successful, and HN2 therapy does not seem to cause a significant prolongation of life.

Circumscribed, inoperable carcinomas of the lung are best treated by x-rays. HN2 appears to be useful when the disease is extensive or severe symptoms are present. There does not appear to be any real evidence that its use in early carcinoma of the lung will significantly check the course of the disease.

In other types of carcinoma and sarcoma transient beneficial results have occasionally been reported, but these effects do not appear to be consistent. Further clinical investigation may disclose conditions in which HN2 will produce some consistent palliation.

Three general points about further indications for the use of HN2 may be considered, as follows:

HN2 does not seem to produce edema in tissues immediately following treatment, such as may occur after x-ray therapy. In obstructive tumors, such as lymphosarcoma pressing on the trachea, or obstruction of the superior vena cava from carcinoma of the lung, HN2 may be indicated prior to x-ray therapy.

Since the effects of HN2 are rapidly exerted it may be used as an emergency measure in selected cases. In patients *in extremis* from advanced but possibly responsive disease — and this situation has arisen chiefly in patients with lymphosarcoma or carcinoma of the lung — HN2 may produce remarkable improvement within twenty-four hours. Subsequently, a more considered program of therapy can then be started.

Studies are in progress to determine the value of combining the systemic effects of HN2 with localized x-ray therapy. In laboratory experiments, it has been shown that if HN2 is given before x-ray therapy an additive effect results; if given in the reverse sequence, x-rays seem to interfere with the action of HN2.[28] On the basis of these laboratory data, it seems reasonable, in the proper situation, to give HN2 prior to x-ray therapy.

Radioactive Iodine

In 1940 Hamilton, Soley and Eichorn[251] demonstrated the selective deposition of radioactive iodine in human thyroid tissue, but only an insignificant amount was found in 2 carcinomas of thyroid origin studied. Metastatic thyroid carcinomas that selectively concentrate radioactive iodine were subsequently described.[252, 253] This concentration of radioiodine produces an intense and destructive local irradiation of thyroid tissue. Functional thyroid tumors are rare, and it is estimated that only about 15 per cent of the tumors of thyroid origin will concentrate iodine.[254] In 19 selected thyroid tumors studied for their ability to take up radioactive iodine, 9 tumors, showing an orderly cell arrangement in a follicular pattern and containing colloid-like material, were capable of concentrating the iodine. These included 5 benign metastasizing strumas and 4 follicular adenocarcinomas. Of the remaining 10 solid alveolar or more anaplastic carcinomas, only 1 showed any evidence of iodine uptake.[254]

Thus far, only 1 patient has been reported in detail as having been treated successfully with radioactive iodine,[255] although additional reports are in press.[256] The selection of patients suitable for radioactive-iodine therapy is made by histologic examination of the tumor and by its ability to concentrate tracer doses of radioactive iodine. In patients with highly functional thyroid tumors, radioactive iodine will concentrate in the metastases. In most cases of functional thyroid tumors, however, the selective uptake of radioactive iodine is not great. The avidity of these tumors for radioactive iodine may be increased in some cases by surgical thyroidectomy, or "medical thyroidectomy" with radioactive iodine.[257] The radioactive iodine generally used is I^{131}, with a half-life of eight days. Large doses up to 200 millicuries have been given during a single course of treatment. The hazards of therapy are due to the radiation effects from radioactive iodine and the rapid destruction of active thyroid tissue.[256] In suitable cases, radioactive iodine will produce extraordinary tumor regressions and relief of pain and disability and will result in considerable prolongation of life. It is emphasized that patients must be carefully selected for treatment, and I^{131} administered with knowledge of the principles of thyroid physiology and radiation effects.

Androgens

Androgenic substances have not been found to have such wide or specific applications as the estrogens in the treatment of cancer. Evidence is now accumulating that they have occasionally a temporary therapeutic effect on osseous metastases from carcinoma of the breast.[226, 228, 258–262] Although only a small number of cases have been reported in each series, certain preliminary generalizations appear justified. The preparation of androgen usually used is testosterone propionate. The premenopausal or younger patients with metastatic mammary carcinoma are considered most suitable for treatment. In about 50 per cent of the patients there will be some subjective improvement, with relief of pain and an increase in activity, appetite and a feeling of well-being. In 20 to 30 per cent of the patients with bone lesions, there will be x-ray evidence of regression and recalcification of the bone metastases. Less commonly, the primary

tumor or soft-tissue metastases will undergo regression.[228, 263] If favorable clinical effects develop, they usually appear within two or three weeks of treatment and continue for variable but often short periods in the range of two to six months. Under testosterone therapy the bone metastases may sometimes remain quiescent while the soft-tissue metastases progress. Data are inadequate for discussion of the relative therapeutic merits of surgical or x-ray castration, alone or in combination with androgen therapy.

A dosage schedule of 100 mg. of testosterone propionate intramuscularly three times weekly has been suggested.[229] This should be given for ten weeks and continued if improvement is satisfactory. The side effects of testosterone administration — masculinizing effects, amenorrhea, edema and increased libido — should be taken into consideration in the decision to initiate therapy. In patients with an elevated blood calcium level prior to treatment, testosterone therapy must be given with caution, since it may further raise the blood calcium to dangerous levels.[259]

Radioactive Phosphorus

Radioactive phosphorus has been used clinically for almost ten years, and its therapeutic applications have been reviewed several times in the past three years.[8, 247, 264–270] There is remarkable agreement concerning the place of this agent in the treatment of neoplastic disease. It has not proved consistently useful in the treatment of Hodgkin's disease and lymphosarcoma, and it is without value in acute leukemia. Its use is chiefly limited to certain disorders of the hematopoietic system.

P^{32} is considered by many to be the treatment of choice in polycythemia vera.[8, 247, 265, 266, 271, 272] It will produce, almost invariably, marked symptomatic relief, a remission in the abnormal hematologic picture and a reduction in the size of an enlarged liver and spleen. The usual duration of remission after an adequate single course of treatment is six to twelve months, but much longer remissions have occurred. The serious complication of P^{32} therapy is hematopoietic injury, with leukopenia, thrombocytopenia and anemia. The usual dose is 4 to 7 millicuries intravenously, and further treatment may be given in one to three months if an adequate response has not been obtained. The agent must be administered cautiously, since the maximum therapeutic and toxic effects usually do not appear before two weeks, and they may not reach maximum development for six months. Furthermore, patients vary markedly in their sensitivity to P^{32}, and an ineffective dose in one patient may be a toxic one in another. There are some reservations about the use of P^{32} in polycythemia vera. Hall and Watkins[266] have suggested that the incidence of acute leukemia is higher in patients with polycythemia vera treated with P^{32}, and Hahn[177] is of the opinion that P^{32} is not necessarily indicated in a disease that is treated so easily and effectively by other methods that have potentially less serious after effects.

In chronic myelogenous leukemia, P^{32} will induce typical clinical remissions, with a fall in white-cell count, rise in hemoglobin, reduction in the size of the spleen and symptomatic improvement. The usual procedure is to administer P^{32} cautiously, perhaps 1 to 2 millicuries twice a week until the white-cell count has begun to fall. One patient may respond to a total dose of 5 millicuries, whereas another may need 25 millicuries. When a clinical remission is induced, treatment is discontinued until relapse occurs.[268] The nature and duration of remissions produced by P^{32} are similar to those from x-rays, and, as with x-ray therapy, P^{32} has only been found to produce a slight prolongation of life.[268] Hall and Watkins[266] have raised the possibility that a greater number of cases of chronic myelogenous leukemia treated with P^{32} terminate more frequently with acute leukemia than those treated by other means. In chronic lymphatic leukemia P^{32}, like other chemotherapeutic agents, does not produce clinical remissions as satisfactory or as consistently as in chronic myelogenous leukemia. In many cases, however, a reduction in white-cell count, decrease in the size of enlarged nodes, liver and spleen, rise in hemoglobin and improvement in the general condition occur. X-ray therapy is more effective in the treatment of large localized manifestations of lymphatic leukemia, but P^{32} is of equal value in the therapy of generalized disease. In multiple myeloma the drug has produced considerable relief of pain in 10 out of 14 patients in one series,[266] but it has not affected tumor growth or altered the progressive course of the disease.

It is apparent that P^{32} is neither unique nor irreplaceable in the treatment of neoplastic diseases of the hematopoietic system. Its fourteen-day half-life sometimes makes the tissue radiation dosage difficult to regulate, and other radioactive isotopes may prove more satisfactory in certain cases.

Urethane

Urethane was first tried clinically by Paterson et al.[146] in the treatment of miscellaneous tumors, including carcinoma of the breast, but the results indicated only slight or inconstant chemotherapeutic activity. Since some of these patients developed leukopenia, the drug was given to patients with chronic myelogenous and lymphatic leukemia and, in these diseases, characteristic temporary clinical remissions were obtained.

Urethane is a drug of low toxicity, and in the past it has been used as a hypnotic. The dose usually recommended for the treatment of leukemia is 2 to 4 gm. daily for two to six weeks or until a therapeutic effect results. It may be given orally[146] in an aqueous solution, by enteric coated capsules or parenterally.[275] Nausea and occasionally vomit-

ing are complications of treatment, but this is rarely sufficiently severe to necessitate cessation of treatment. Larger doses up to 15 gm. a day have been given.[27] The large doses have a hypnotic and moderately intoxicating effect. The results of excessive urethane therapy have not been definitely established, but the drug should be administered cautiously and the hematologic picture carefully followed. In patients with leukemia there is no doubt that urethane will produce a severe depression of the bone marrow.[146, 273] It seems likely that patients with normal bone marrow exposed continuously to large doses of urethane will show hematopoietic injury, with leukopenia, anemia, thrombocytopenia and bleeding. Moeschlin,[148] however, has been unable to produce any injury to the bone marrow of normal male patients by the continuous administration of urethane. Urethane has a moderately cumulative effect, and its hematologic action in leukemia varies with the total amount and the daily dosage of the drug administered. No evidence has been presented that urethane induces pulmonary adenomas in man, although this possibility must be considered.

Since the initial publication on the clinical effects of urethane in leukemia, several confirmatory reports have appeared.[273–276] The most successful results have been obtained in chronic myelogenous leukemia. Within one to three weeks after urethane treatment was begun, there was, in almost all cases, a fall in the white-cell count, a tendency of the differential to return toward normal, a rise in the hemoglobin and a reduction in the size of the spleen. The total dose required to accomplish this ranged from 19 to 325 gm., and remissions usually occurred within ten to thirty-one days. Patients relapse under treatment, however, and there is no evidence that life is appreciably prolonged or the course of the disease altered by the treatment. Patients in the terminal stage of chronic myelogenous leukemia do not respond well to urethane. In chronic lymphatic leukemia the results in general have not been so satisfactory as those in myelogenous leukemia, although in the majority of cases treated, a temporary remission of the disease has been induced, with regression in the size of diseased organs, a rise in hemoglobin level, a decrease in the white-cell count and an absolute increase in the polymorphonuclear leukocytes. In Paterson's[274] series 13 out of 23 patients showed improvement, 5 were unaffected, and 5 became worse. In a smaller series of 8 cases, Hirschboeck et al.[275] observed a satisfactory remission in 3 cases, a fair result in 2 and poor results in the remainder. No significant clinical improvement has been observed in acute leukemia, although the white-cell count may be lowered. There have been no consistent results from the use of the drug in lymphosarcoma or Hodgkin's disease.[146, 275] A remarkable remission in an anaplastic carcinoma metastatic to the skin has been reported.[277] In 4 patients with prostatic carcinoma no longer responding to hormonal control, large doses of urethane caused some shrinkage of the primary tumor, a decrease in acid phosphatase, a relief of pain and a sense of well-being.[278] One of these patients died of hepatic necrosis, which could not definitely be attributed to the urethane therapy.

In general, in the treatment of chronic myelogenous and lymphatic leukemia, urethane can be expected to produce remissions similar to those effected by x-ray therapy, radioactive phosphorus, nitrogen mustard and Fowler's solution.[275] Its action is perhaps not so consistent, precise and predictable as that of the more toxic agents, and it is unlikely that urethane will be effective in patients in whom these other agents fail. Furthermore, at effective doses, it has a toxic effect on the bone marrow and should, therefore, be administered cautiously.

Fowler's Solution

Although there are no recent papers on the use of potassium arsenite in leukemia, it is well established as a useful agent for inducing clinical remissions in early and responsive cases of chronic myelogenous and lymphatic leukemia.[279]

* * *

Only a small group of human neoplastic diseases is susceptible to the palliative effects of chemotherapeutic agents. In carcinoma of the prostate estrogens may temporarily halt the disease and prolong life; in an occasional patient with carcinoma of the thyroid gland radioactive iodine is effective in interrupting the disease and prolonging life; in Hodgkin's disease nitrogen mustard serves as a useful adjuvant to x-ray therapy, and this appears to be true, but to a lesser extent, in lymphosarcoma and mycosis fungoides; in chronic myelogenous and chronic lymphatic leukemia Fowler's solution, urethane, nitrogen mustard and radioactive phosphorus are all capable of inducing clinical remissions when the patient is responsive to therapy, but they are all uniformly less effective when the patient approaches the terminal or acute stage; in polycythemia vera radioactive phosphorus and, possibly to a lesser extent, nitrogen mustard will induce excellent clinical remissions; in carcinoma of the lung nitrogen mustard may produce transient palliative effect; and in mammary carcinoma in postmenopausal patients estrogen therapy may produce temporary palliation and tumor regressions — in the premenopausal patient with osseous metastases androgens are more effective. Inconstant and unpredictable transient responses to some of these chemotherapeutic substances have been reported in a variety of other tumors.

It is to be hoped that in future reviews the great efforts of the laboratories and clinics in cancer therapy will result in a longer list of neoplastic diseases responsive to more effective chemotherapeutic agents.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 34341

PRESENTATION OF CASE

A forty-eight-year-old hide merchant was admitted to the hospital because of abdominal pain.

The patient developed vague, epigastric discomfort and nausea approximately forty-eight hours previous to admission following the ingestion of food. This subsided soon but recurred each time he ate. Three hours before admission the pain became severe, cramping and localized in the midabdomen, and was accompanied by vomiting. At times borborygmus was audible to the patient.

Approximately one year before admission an appendectomy was performed at another hospital. It was said to be a difficult operation and there was a question of the appendix having ruptured. An abscess of the abdominal wall complicated his convalescence. Three months after this the patient began having difficult bowel movements with occasional diarrhea and intermittent lower abdominal pain. A physician at this time noted a firm, tender mass in the right lower quadrant. The stools were not bloody or tarry. For several months before admission the patient had intermittent chills and fever. X-ray studies of the entire gastrointestinal tract six months before entry were reported to be negative. Three and a half years previous to admission the patient had a coronary occlusion. While convalescing from this he had one episode of hematemesis and repeated tarry stools presumed to be due to a peptic ulcer.

Physical examination revealed a pale man in no acute distress. The heart and lungs were normal. The abdomen was tympanitic. In the right lower quadrant a mass extended from beneath the appendectomy scar toward the pubis. It was 8 to 10 cm. in diameter, firm, fixed and somewhat tender. There was also diffuse tenderness in the epigastrium. Peristaltic sounds were high-pitched. Bilateral, easily reduced inguinal hernias were present.

The temperature, pulse and respirations were normal. The blood pressure was 125 systolic, 75 diastolic.

The urine had a specific gravity of 1.026 and gave a ++ test for albumin, and the sediment contained frequent hyaline casts and 4 pus cells per high-power field. Examination of the blood disclosed a hemoglobin of 15.5 gm. and a white-cell count of 15,100, with 90 per cent neutrophils. A stool specimen was guaiac negative. An electrocardiogram was suggestive of an old posterior myocardial infarct. An x-ray film of the abdomen showed gas scattered throughout the large bowel, and there appeared to be two dilated loops of small bowel in the midabdomen.

The patient was given fluids intravenously, and a Miller–Abbott tube was passed.

An operation was performed on the second hospital day.

DIFFERENTIAL DIAGNOSIS

DR. HENRY H. FAXON: Shall we review the x-ray films, Dr. Wyman?

DR. STANLEY M. WYMAN: The loops of dilated bowel, apparently small bowel, are seen in the left middle and lower abdomen. I cannot see the gas described in the colon. There is a large collection of gas in the right upper abdomen, the location of which I cannot determine. This shadow may represent ileum but is probably colon; at least there are very few haustral markings. The stomach is seen in the upper midabdomen. There is an absence of any great degree of gas in the right lower abdomen, but there are a number of small collections of gas, the locus of which is not certain, and the appearance is quite atypical. The film taken the next day again shows several loops of gas-containing small bowel that do not appear so widely dilated as those at the last observation. Here again there are small collections of gas in the right lower abdomen in a rather atypical pattern.

DR. FAXON: Could this gas be free in the peritoneal cavity?

DR. WYMAN: I do not believe so.

DR. FAXON: Could the strange patches of gas that you speak of be in the subcutaneous tissue?

DR. WYMAN: They suggest gas outside the bowel somewhere, and they are quite consistent with what is seen in abscess.

DR. FAXON: Is there any gas in the rectum?

DR. WYMAN: No.

DR. FAXON: Can you see the kidney shadows?

DR. WYMAN: The left kidney shadow is quite well outlined; the right is less well outlined. Both are normal in size, shape and position.

DR. FAXON: The case falls into two separate parts: the nature of this chronic mass in the right lower quadrant and the acute episode that precipitated the hospital entry. Apparently, the mass appeared approximately nine months before entry, for he was operated on one year before entry and it was three months later that his doctor discovered a mass in the right lower quadrant. It is rather

surprising that more intensive studies had not been done to determine the correct diagnosis in the intervening months. So far as the mass in the right lower quadrant is concerned, it seems to me that we have to consider two main classifications — a tumor or an inflammatory mass. If a tumor, it may have been of the bowel or retroperitoneal space. In favor of its being a tumor is its long persistence with relatively little change. The age and general appearance of the patient are consistent with a malignant lesion of the right colon or of the bowel, and the law of averages favors its being a neoplasm. I mention this because I think that the burden of proof lies on the person who says that this was not a growth of some kind. Did he have a barium enema?

DR. WYMAN: No.

DR. FAXON: When one is in doubt a barium enema carries with it little risk and often gives much helpful information. The mass, from the description, seems to be fairly anterior and not to lie deep in the pelvis. X-ray studies should have been repeated even if they were negative six months before. It is notorious and readily admitted that the right colon is the portion of the gastrointestinal tract in which it is especially hard to visualize a malignant growth by x-ray study. The fact that six months before entry the mass was present and the roentgenologists were unable to say if it was an intrinsic lesion of the bowel does not rule out the possibility of its being inherent in the intestine but makes such localization of the lesion most unlikely.

There are a few points against the diagnosis of a malignant growth. In the first place if it had been of the bowel and possibly missed by the earlier x-ray examination, the patient should have shown anemia. Right-sided lesions are notorious for the anemia that they cause. But here we have a case in which examination of the stool was negative and the hemoglobin was 15.5 gm., although this may be accounted for in part by dehydration. We are not told how much he vomited.

The second argument against neoplasm is that within three months after the previous operation a mass was felt for the first time and had grown to a size that was easily palpable by the patient's physician. The description of the difficulties encountered by the surgeon suggest that the first operation very obviously might have been misdirected, and although he took the appendix out it is possible that the essential disease was neither dealt with nor recognized.

It could, of course, have been a retroperitoneal lymphoma, but again I think it is unlikely that the patient would have remained in such apparently good condition over such a long period.

In considering the second possibility, that the mass in the right lower quadrant was inflammatory, it should be pointed out that the symptoms started as those of irritation of the lower bowel, with diarrhea and difficult bowel movements. The diarrhea and intermittent lower abdominal pain could have been caused by extrinsic pressure or infection on the lower bowel. This antecedent inflammatory process for which the patient had been operated upon would have given cause for the subsequent development of an inflammatory area in the right lower quadrant. We know that pus had been present in a sinus and that the wound had become infected and drained for a considerable period. It is interesting that the wound eventually healed, which would be unlikely with tuberculosis, actinomycosis or a spreading type of infection. He had chills and fever for several months, which again suggest an inflammatory process. The temperature was normal at the time of admission here, but I do not believe that would change our premise that this was an inflammatory mass, which had been present so long and was so completely walled off that he might have evinced his hyperthermia earlier and reached the stage where he had little or no fever. He had an elevated white-cell count, and of even more significance is the fact that the smear showed 90 per cent neutrophils. There is therefore much to suggest that this was an inflammatory lesion. The absence of blood in the stools is consistent with a mass outside the bowel, which I am postulating may well have been inflammatory. However, if it was an inflammatory process of the usual variety, it should not have persisted this long unless either some recurrent cause for the infection existed or a very unusual type of infection such as tuberculosis, actinomycosis, regional ileitis or diverticulitis was present. A foreign body might have been keeping the inflammation going. The patient was rather old for regional ileitis, and although diverticulitis often gives this type of picture it is in the left lower rather than the right lower quadrant. Meckel's diverticulum has little to recommend it as a diagnosis. Volvulus or intussusception would not have lasted this long. A foreign body, left at the previous operation, could quite readily have caused an inflammatory mass of this nature. A fecalith from the ruptured appendix might have persisted for a long time and would have kept an inflammatory reaction going.

I do not believe the mass on the right side was kidney; it seemed too low, and there was not enough wrong with the genitourinary tract to make it seem likely that that was the cause of the lesion. I do not believe the gastric ulcer three years previously was more than an incidental finding of the past, nor do I think that the inguinal hernia or the coronary disease had anything to do with the picture.

Regarding the symptoms that brought him into the hospital, I think that they were typical of small-bowel obstruction, in which there is either a paralytic, inflammatory type of obstruction, such as

occurs in general peritonitis following ruptured appendix, or a mechanical obstruction. This man had plenty of reason for mechanical obstruction, both by the mass that was present, which might have involved the small intestine, and from the previous peritonitis, which might have left bands that could cause kinking. If this obstruction had been on a paralytic basis, the patient should have been sicker than he was and should have had absent peristalsis, and the abdomen should have been rigid. Furthermore, there should have been some good etiology such as a perforated ulcer, which I think in this case is highly unlikely. I do not believe that he fits the picture of a dynamic ileus. On the other hand, with mechanical obstruction of the small bowel, a patient is not of necessity especially ill until obstruction has gone on for such a long time that there is increased high-pitched peristalsis, persistent vomiting and dilated loops of small bowel by x-ray examination. Although it is tempting to say that this man had small-bowel obstruction, secondary to a neoplasm or a growth of some kind, I shall put down as my diagnosis mechanical small-bowel obstruction secondary to an inflammatory mass in the right lower quadrant caused by and persisting because of a foreign body retained at the first operation.

Clinical Diagnosis

Inflammatory lesion, region of cecum, due to regional enteritis or foreign body.

Dr. Faxon's Diagnosis

Small-bowel obstruction due to inflammatory mass caused by foreign body.

Anatomical Diagnoses

Carcinoma of stomach, with peritoneal metastases.
Small-bowel obstruction.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Claude Welch, who operated on this patient, is operating and unable to get here. He called me on the telephone, however, just before the conference and asked me to say that his preoperative diagnosis was an inflammatory lesion in the region of the cecum due (first choice) to regional enteritis or (second choice) to a retained foreign body. He was forced to operate on the patient without complete study because of the inability to control the intestinal obstruction in any other way.

At operation he found a mass in the region of the cecum, which appeared to be granulomatous and inflammatory. There were also, however, some nodules seen on the peritoneal surface elsewhere. When he explored further he found a large tumor mass in the pyloric portion of the stomach, occupying most of the lesser curvature. He felt reasonably sure from palpation that it was a neoplastic lesion in the stomach. He was still inclined to think that the lesion in the region of the cecum was inflammatory. He took a biopsy from that and also from one of the peritoneal nodules, and both showed metastatic carcinoma. He relieved the intestinal obstruction by doing a side-to-side anastomosis between the ileum and the sigmoid, since the lumen of the entire ascending colon was compromised by a mass, whatever it was. Subsequent x-ray examination of the stomach was done. That showed a fairly characteristic picture. Dr. Wyman will show the films.

Dr. Wyman: The film demonstrates fairly well an annular carcinoma involving the distal third of the stomach.

Dr. Faxon: Do you suspect that the bleeding of three years previously was related to the lesion found in the stomach at the time of operation?

Dr. Mallory: Probably.

Dr. Welch has just arrived. We have just finished discussing your case, and Dr. Faxon's diagnosis was an inflammatory lesion of the cecum, probably secondary to retained foreign body.

Dr. Claude E. Welch: I am sorry that I missed his discussion. I think that I might answer any questions that may have been raised by the brief summary of a quite confusing case. The things that impressed us before operation were the inflammatory mass in the right lower quadrant and the signs of intestinal obstruction, the history of which was rather chronic. We thought the best way to put the whole story together was on the basis of regional enteritis that had perforated, forming an abscess, first intraperitoneally and then perforating into the abdominal wall. We were not very happy about the diagnosis, but we had to operate on him on that basis.

Dr. Faxon: Have you seen many cases of regional enteritis in this age group?

Dr. Mallory: It usually occurs in the twenties, although we do see it occasionally in older patients.

Dr. Faxon: As a matter of curiosity, were the x-ray films of the gastrointestinal tract taken six months prior to operation reviewed?

Dr. Wyman: They have been since, and they appeared to be entirely normal.

CASE 34342

Presentation of Case

A forty-six-year-old man entered the hospital because of hematuria.

The present illness began five weeks before admission with anorexia, nausea and occasional vomiting. At the same time he noted some red spots on his skin. These came and went and were slightly itchy but never tender. Four weeks before admission the urine was noted to be pink, and this sign also fluctuated in degree during the succeeding

period. Three weeks before admission the family physician discovered albumin and red cells in the urine. No history of other abnormal bleeding could be elicited, and there were no other urinary symptoms. There had been some ulcer-like abdominal pain in the past, but this was not a part of the present illness nor were there any chills, fever or severe malaise.

The past history disclosed rheumatoid arthritis, which had bothered the patient for eight years prior to admission but had never caused any severe pain or disability. Three years before admission a diagnosis of pulmonary tuberculosis was made. The disease was treated by thoracoplasty and considered quiescent one year later. There was no history of rheumatic fever, scarlet fever or kidney disorders.

Physical examination showed a well developed and well nourished man sitting up in bed. On the skin there were purplish, nonblanching spots in small clusters and larger ecchymotic spots chiefly over the lower legs. The mucous membranes and nailbeds were clear. The thoracoplasty wound on the left side was well healed. The breath sounds were slightly depressed on the right, but no rales or areas of dullness were made out. The heart was normal except for a Grade II basal systolic murmur heard best along the left sternal border. The liver edge was felt slightly below the costal margin; otherwise examination of the abdomen was negative. Rectal examination was also negative. The hands and feet showed slight rheumatoid changes.

The temperature, pulse and respirations were within normal limits. The blood pressure was 120 systolic, 75 diastolic.

Examination of the blood disclosed a hemoglobin of 9.4 gm. and a white-cell count of 13,500, with 84 per cent neutrophils. The urine showed a specific gravity of 1.008, gave a +++ test for albumin, and the sediment was "loaded" with red cells. A stool specimen was guaiac negative. Culture of the sputum grew a rare beta-hemolytic streptococcus and abundant colonies of *Neisseria catarrhalis*; a concentration was negative for acid-fast bacilli. Culture of the urine grew a few colonies of *Staphylococcus albus*. The sedimentation rate was slightly elevated. A tourniquet test was negative. The nonprotein nitrogen was 136 mg., and the total protein 6.1 gm. per 100 cc., with an albumin-globulin ratio of 1.78. The carbon dioxide was 21.3 and the chloride 84 milliequiv. per liter. The prothrombin time was 20 seconds (normal, 17 seconds). A congo-red test was unsatisfactory. X-ray examination of the chest showed the thoracoplasty on the left, fibrosis with emphysematous blebs throughout both lungs and a soft mottling at the left hilus extending inferiorly. Retrograde pyelograms showed a faint, irregular calcification overlying the upper third of the left kidney just above the middle calyx, and constant beading of the ureters.

In the hospital the patient's symptoms continued unchanged, and he developed hemoptysis, which gradually increased in severity until considerable respiratory difficulty was produced and clots were raised. On auscultation of the lungs numerous rhonchi and moist medium rales were heard throughout, and a chest plate showed extensive mottling in both lung fields. On the ninth hospital day his condition deteriorated rapidly, the pulse and respirations rising although the blood pressure remained stable and the temperature was normal. He died the same day.

Differential Diagnosis

Dr. Reed Harwood: Let us look at the x-ray films.

Dr. Stanley M. Wyman: This is the old left thoracoplasty involving the upper ribs, and marked collapse of the upper half of the lung field is well demonstrated. The diaphragm is low in position, being at the level of the twelfth rib. There is fibrosis throughout both lung fields, most marked in the upper portion of the right. There is probably a small quantity of fluid or possibly thickened pleura at the right base, and a fine, indefinite mottling in both lung fields, which may represent edema. The heart shadow itself is not remarkable. The film taken five days later shows this extensive, very pronounced change with a heavy, granular density throughout the central portions of both lung fields, sparing only the bases and the portion under the thoracoplasty. The area of calcification in the left kidney is fairly well demonstrated. The lesion in this area when injected with dye is seen to be present in the middle and upper calyxes. The remaining calyxes are normal in appearance, and the beading of the ureter is well seen. The spleen appears to lie unusually low and is probably enlarged. The liver also extends well down and is also probably enlarged. The right-kidney calyxes and pelvis appear normal, but there are two or three small areas suggesting beading in the ureter.

Dr. Harwood: Is this picture typical of the kind of pulmonary edema that one often sees in uremia?

Dr. Wyman: Yes; it appears to be quite consistent.

Dr. Harwood: What is the significance of the beading of the ureter?

Dr. Wyman: It is usually thought to mean old infection, such as tuberculosis. In keeping with that is the calcification apparently in the kidney parenchyma.

Dr. Harwood: We are faced with the problem of making a diagnosis of what type of renal disease this patient had. What combination will commonly give nitrogen retention and hematuria? Cancer we can satisfactorily exclude. Amyloid disease was thought of in this case, but I believe

that hematuria is an unusual manifestation of amyloid disease. Prostatic hypertrophy and obstruction can produce hematuria and uremia, but there is no evidence of difficulty in urination in this case and no difficulty in passing the cystoscope. I think that that can be excluded. It is said that at least 10 per cent of patients with pulmonary tuberculosis have lesions in the kidney of greater or less severity. We cannot exclude the presence of tuberculosis in this patient. Indeed, I think it likely that he did have a tuberculous lesion of the left kidney. Hematuria, of course, is a common symptom of this disease, but there is another characteristic of renal tuberculosis — namely, that despite considerable destruction of the renal parenchyma, renal failure is rare. Furthermore, most cases of advanced renal tuberculosis also have tuberculosis in the bladder, which can be readily excluded by cystoscopy in this case, and by the lack of symptoms of cystitis. Pyelonephritis is another condition in which hematuria and albuminuria and nitrogen retention are found. It is distinctly unusual, though, to have blood alone without pus in the urine and very unusual not to have fever and cystitis. I therefore think that pyelonephritis is unlikely. Glomerulonephritis is next to be considered. Of course glomerulonephritis will produce hematuria and nitrogen retention. Casts are also commonly found in glomerulonephritis, but they are not mentioned in the record of the case under discussion. Hypertension, generalized edema and retinal hemorrhages were absent in this case. I do not believe that we can exclude the possibility of glomerulonephritis with terminal uremia, but it is unlikely.

The skin lesions may be an important clue. They suggest to me the possibility of two diseases: Henoch's purpura and periarteritis nodosa. A recent review of Henoch's purpura by Gairdner* tells us that joint and skin lesions are the commonest manifestations of Henoch's purpura. Most cases also show evidence of renal involvement, and some patients die in renal failure. It is significant that the cases reported all show macroscopic hematuria. The condition usually occurs in young people, although cases have been reported in later life, and it is more common in males than females. Death from renal failure is not uncommon, and it is of interest that the autopsy reports show "glomerular nephritis." The negative tourniquet test in this patient does not exclude the diagnosis of purpura because sometimes the tourniquet test is positive. Possibly against the diagnosis of Henoch's purpura is the total absence of lesions of the gastrointestinal tract. Cases have been reported, however, in which only renal disturbance has been noted.

*Gairdner, D. Schönlein-Henoch syndrome (anaphylactoid purpura). *Quart. J. Med.* 17:95-122, 1948.

Periarteritis nodosa can involve any arteries in the body, and it is perfectly possible that the vessels of the kidney and skin were involved in periarteritis nodosa in this case. The absence of eosinophilia is possibly against this diagnosis. I have the feeling that this patient died of a generalized vascular disturbance. As Gairdner points out, the three conditions under discussion — purpura, periarteritis and nephritis — are closely allied in some respects, both pathologically and possibly etiologically. In my diagnosis I place Henoch's purpura as my first choice, periarteritis nodosa as my second, and acute glomerulonephritis as my third.

DR. ALFRED KRANES: Are you able to make a diagnosis of Henoch's purpura anatomically?

DR. TRACY B. MALLORY: I do not know how to.

DR. DONALD S. KING: Would you get that much hemoptysis from pulmonary edema, Dr. Harwood?

DR. HARWOOD: How much was there?

DR. KING: The patient raised clots.

DR. JACOB LERMAN: One occasionally sees that much in rheumatic heart disease, but there is no evidence of that here.

DR. KING: That is right, but this man had no mitral stenosis. Does hemoptysis occur in purpura?

DR. HARWOOD: It must be distinctly unusual. I could find no mention of it in the literature.

DR. KING: I cannot remember having seen any. I would almost have to get an infarct into this case to explain the hemoptysis.

DR. HARWOOD: I would not go any farther than to say that it was a terminal event.

DR. KING: Most of the cases here are that.

DR. HARWOOD: I mean that the patient did not die from the hemoptysis.

DR. PAUL C. ZAMECNIK: I think it is interesting that the purpura seemed to follow the scratch marks and that the purpuric spots did not fade very quickly. I saw them one day and about two days later they had not changed. The patient seemed to run a strikingly rapid downhill course. He was admitted on the genitourinary service with a question of renal stone. Once that was ruled out he was transferred to the medical service. It is interesting that at the time I saw him the nonprotein nitrogen was 100 mg. per 100 cc. He was relatively symptom free, and four days later he died. We had the feeling that we were missing something all along, but all we could put our finger on was the renal damage. In the absence of anything else we said it was acute or subacute glomerulonephritis.

DR. LERMAN: In the presence of tuberculosis, as this kidney suggests, amyloid disease is always a good bet.

DR. HARWOOD: He may have had some, but do you believe that he died from it?

DR. LERMAN: No; he might have bled from the tuberculous focus in the lung.

DR. KING: That is what I was wondering about. Old tuberculous lesions with thoracoplasty bleed. However, we have no evidence for it.

DR. MALLORY: It was strongly considered on the wards to account for the hemoptysis.

CLINICAL DIAGNOSES

Pulmonary tuberculosis, with hemorrhage.
Subacute glomerulonephritis.

DR. HARWOOD'S DIAGNOSES

Henoch's purpura.
Periarteritis nodosa?
Acute glomerulonephritis?
Uremia.
Pulmonary edema.

ANATOMICAL DIAGNOSES

Subacute glomerulonephritis.
Pulmonary edema, with massive hemorrhage into lungs.
Purpura.
Pulmonary tuberculosis, healed.
Operation: thoracoplasty, left.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The striking lesion found at autopsy was in the kidneys. They were considerably enlarged, weighing 510 gm., with a grayish yellow cortex and peppered over with small red spots — a typical picture for subacute glomerulonephritis. That was confirmed microscopically. The only other findings of great interest at autopsy were in the lungs, and they were somewhat difficult to interpret.

The tuberculosis was on the whole very well healed. We found only two or three quite small lesions that showed any degree of activity, but none of them we felt could be responsible for the hemorrhage. On the other hand, the entire right lung and the uncollapsed portion of the left lung were filled with blood. Parts of this were of an almost solid consistence, practically consolidated; other parts were more fluid — a hemorrhagic lung with pulmonary edema.

Microscopical examination showed massive hemorrhage into the alveoli and rather minimal inflammatory reaction. There was some fibrin, some foci of hyaline menbrane lining the alveoli and a beginning exudation of polymorphonuclear leukocytes. The inflammatory reaction looked more as if it were a reaction to hemorrhage than if it were primary. I am inclined to interpret this as a form of extremely severe pulmonary edema or pneumonitis, which we do see from time to time in cases of active nephritis. I have seen it most often in cases of sulfonamide injury to the kidney, but I am quite sure that I have seen it in glomerulonephritis on a number of occasions as well. Whether there actually exists an entity that we call pneumonitis, I am not sure. I have been tempted sometimes to think that there might be one. The picture is both grossly and histologically very similar to what is seen in a certain number of cases of acute rheumatic fever and ordinarily called acute rheumatic pneumonitis. I do not believe I can differentiate the two on the microscopical slides.

DR. KING: There is a hemorrhagic form of pulmonary edema with hemoptysis?

DR. MALLORY: Yes; one sees it occasionally.

DR. KING: It is rare.

A PHYSICIAN: Were there any casts in the urine?

DR. JAMES DAVIS: Two urine specimens were searched for casts, but we found none — only red cells.

A PHYSICIAN: Were there any lesions in the ureter?

DR. MALLORY: No.

A PHYSICIAN: How are the skin lesions accounted for?

DR. MALLORY: Purpura is not rare with renal insufficiency. I would assume that that was the cause of it.

DR. HARWOOD: Gairdner reports a specific pathologic picture in Henoch's purpura as opposed to other kinds of bleeding in the skin; it might be interesting to know what the skin lesions showed histologically.

DR. MALLORY: The skin lesions were not examined. One frequently discovers that skin lesions that are conspicuous during life are hardly visible by the time of autopsy. Unless our attention is specifically called to them, we are apt to miss them.

DR. ZAMECNIK: Is there a pathological distinction in the kidneys between acute glomerulonephritis and purpura?

DR. MALLORY: I think there would be no question about that. I see no reason why one should have active lesions — the crescent formation and so forth — in purpura.

A PHYSICIAN: Did the blood pressure go up?

DR. MALLORY: No; not in the period of observation. Of course that is unusual for glomerulonephritis, I must admit.

A PHYSICIAN: Was there any lesion in the spleen?

DR. MALLORY: No; in the bone-marrow sections the megakaryocytes showed an unusual amount of pyknosis and degenerative change. Otherwise the bone marrow was not normal; it was a little hypoplastic.

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DOWN EAST DOCTOR

MARY ELLEN CHASE, professor of English at Smith College, is a coast of Maine New Englander, a product of the sturdy traditions and the independence of that particular rock-bound section of the country's shore line. That she should read the Aphorisms of Hippocrates in the original Greek or deliver the address at the annual dinner of the Massachusetts Medical Society is no more unusual than that she should have grown up and left the region of Penobscot Bay to teach English in a leading woman's college. Women of the Maine coast are accustomed to doing a day's work in fair weather or foul.

Professor Chase's recollections of the character and activities of a country doctor a generation ago will stir nostalgic memories in many who read her address in this issue of the *Journal*, for it deals with a period and a place whose spirit is that of hardihood and self-reliance and personal independence. The smells of harness leather and the grain bin still linger in the nostrils of many of her countrymen who have not yet passed their active years; other ancillary facilities of transportation contributed to the "smell" of the doctor, as Miss Chase so nicely phrased it — the carriage lap robe, sun-cured hay and, at times, that Augean aroma that characterizes certain phases of the nitrogen cycle conspicuously identified with hooved animals. There are frontiers, too, where cold drawn castor oil and sweet spirits of niter are still in daily use, and the onion poultice has been professionally applied within the memory of living man.

The costs of medical care rarely constituted a problem in the country districts a generation ago, — Miss Chase's family spent $105 for medical care over a period of sixteen years, — and pay was likely to be in "kind" — in labor or lobsters, a load of wood or a barrel of potatoes. The practice of medicine was not entirely a profession; it was a way of life, as farming once was, and a kindly one.

Miss Chase's reminiscences furnish something besides entertainment; they are more than a pleasant interlude in one of memory's lanes. They are a reminder that the medicine of today, if it is to be effective and economical, must be brought to the patient through the medium of one who is both counselor and friend. More and more, as life becomes increasingly complicated and the science of medicine more intricate and more costly it is apparent that the resourceful family doctor must remain as the backbone of the profession. Medicine in its relation to its public and in the service that it can economically deliver will be on firmer ground if the family doctor is encouraged to resume his former pastoral position.

The greater the complexities of medical science and the greater the need for specialization on that account, the greater also is the need of the patient for wise and kindly guidance. If the family practice of medicine should disappear, a great loss would be sustained. Such a loss would also mean that a type of life in which these values were appreciated had gone.

POLYMYXIN

THE almost universal tendency of streptomycin to give rise to resistant organisms, its significant toxicity and its relatively low activity against many common pathogens have resulted in a very intensive search for new antibiotics to replace streptomycin in the fields in which it has proved its greatest use — namely, against gram-negative bacilli and in tuberculosis. At least one agent, highly active against gram-negative bacilli, has become available and is having some clinical trials. This agent has been obtained in two separate laboratories[1, 2] in this country from several strains of *Bacillus polymyxa* and a very similar if not identical substance was obtained in England[3] from a related organism, *B. aerosporus*. Interestingly enough, the findings in all three laboratories were announced almost simultaneously.

The preparation, named polymyxin by the workers at the American Cyanamide Company and aerosporin by those of the Wellcome Laboratory, has interesting properties.[2, 4-7] It is a basic substance obtainable in the form of crystalline hydrochloride and is water soluble. Its activity is not affected by reactions between pH 2 and 7 and is only slightly affected by blood, serum or other mediums at physiologic ranges. Polymyxin is effective against a number of important gram-negative bacilli including brucella, salmonella, *Haemophilus pertussis*, *Ebertbella typhosa* and *Escherichia coli*. It is active in low concentrations more like those of penicillin rather than those of streptomycin within their respective fields. It is not active against gram-positive organisms, fungi or mycobacteria, and most strains of proteus are not inhibited. It is active in mice when given subcutaneously against infections with *Klebsiella pneumoniae*, *H. pertussis*, *Salmonella typhi*, *H. influenzae* and *Brucella bronchoseptica*, and it is also effective against fowl typhoid in chicks. It is not effective orally, but when given by this route, it results in replacement of sensitive by insensitive organisms in the feces.

Polymyxin is relatively nontoxic, but the hydrochloride may produce local irritation, and there is some evidence of a histamine-like contaminant and possibly renal tubular damage from some preparations except possibly those that are highly purified. Resistant strains are not obtainable by the methods that readily produce streptomycin-resistant organisms, but resistance may be increased in vitro by serial passage, though much more slowly than with streptomycin. No morphologic changes result in the organisms. Polymyxin is equally effective against streptomycin-sensitive and streptomycin-resistant strains, and, contrariwise, streptomycin is equally active against strains made resistant to polymyxin as against their parent strains.

The action of the agent is apparently very rapid and is considered to be bactericidal at least when adequate concentrations are used. It is apparently well absorbed from parenteral routes but seems to have a high renal threshold.

Only one published report of the use of aerosporin in England is available.[8] The agent was used in the treatment of 10 cases of pertussis, and though the author appeared to be enthusiastic about the effects, the results as reported are difficult to interpret and are certainly far from convincing. There was some evidence of renal toxicity, and coexisting urinary-tract infections did not seem to be influenced favorably.*

Obviously, more data are necessary before evaluation of this compound or of these agents, if they are different. The effectiveness and toxicity in further clinical trials of pure preparations are therefore being awaited. The only other intimation of beneficial effects in a number of infections in human beings is a brief mention of cases of infections due to *Pseudomonas aeruginosa*, *K. pneumoniae*, *H. pertussis* and *B. abortus* in which there was definite evidence of the therapeutic effectiveness of polymyxin.[9]

It is obvious that a better agent than streptomycin is needed in the treatment of infections due to the Friedländer bacillus, salmonella, brucella, pertussis and other gram-negative organisms. It will also be of interest, in view of preliminary indications of the high renal threshold, to know whether this agent is effective in the treatment of urinary-tract infections. The possibility of the development of resistant strains during treatment

*A preparation called polymyxin B has recently been made available for clinical trials and is alleged by the manufacturer to be free of toxic effects on the kidneys.

must also be known before enthusiasm for this agent is engendered.

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NEW FASHIONS IN WOODEN LEGS

MAN'S mechanical ingenuity is a strange and wonderful thing. Not content with devising ever better methods for blowing off human arms and legs, he ceaselessly toils to perfect artificial means of replacing them. When, in the sixteenth century, bombards and hand-cannon came into more effective use on the battlefield it probably appeared to contemporary observers that scientific progress was entering a deplorable time of inhuman destructiveness. It then took a doctor to turn science into a more humanitarian channel. In 1564 Ambroise Paré published his first account of artificial limbs with joints that worked by springs and ratchets.

As the science of destruction continued to advance, so also did the science of replacing limbs, but to a more modest extent. Ravaton, White, Addison, Wilson, Brunninghausen, Ruhl, Miles, Serre and others did their best to keep Paré's crude inventions abreast of the times. The recent bound forward that civilization has taken in the development of land mines, blockbusters and atomic explosions is now placing an unprecedented strain on humanitarian inventiveness.

It is reassuring to know, however, that the race is not being abandoned. On May 13, 1948, the armed forces, Veterans Administration and Committee on Artificial Limbs of the National Research Council held a demonstration of the newest prosthetic developments at the National Academy of Sciences in Washington, D. C. Not the least impressive feature of the Government's artificial-limb program is the list of high-powered names and agencies concerned. Though reminiscent of less immediately altruistic activities, such names as Vannevar Bush, Robert Patterson, Northrop Aircraft, Wright–Patterson and Naval Ordnance Laboratory assure at least the degree of scientific competence that was directed toward producing amputees on so large a scale.

The devices now ready for field testing prior to general production and distribution are as far ahead of Paré's as the atomic bomb is ahead of the bow and arrow. "Some involve rather radical principles of design," according to the official report. For example, a prosthesis for above-the-knee amputations incorporates "control of knee flexion by a hydraulic cylinder with unbalanced valve activated by muscle control": "Coordination of knee and ankle motion includes initial knee flexion on heel impact with partial knee extension during the load phase (due to a crossed linkage including the hydraulic cylinder) as well as toe pickup during the swing phase (due to a rod with hydraulic slip joint)." In another, "control of knee flexion is provided by a vane-type hydraulic snubber with valve closed by pressure on rear half of foot regardless of ankle position." Full advantage has been taken of flexible plastics to produce artificial hands of naturalistic appearance whose mechanism permits "fast fanning of fingers until they press the load against the thumb, then engagement of a force multiplier for increased grip" and an "automatic lock with anti-backlash device driven by the single control cable."

There can be no doubt about the technologic triumphs represented by these exhibits. How well they will all serve the needs of their recipients remains to be seen. Apparently, Paré had mental reservations concerning some of his own devices because he included the simple design of a peg leg, as he says, "for poor people." Certainly Long John Silver on Treasure Island and Silas Wegg in Dick-

ens's London did not let their peg legs curtail their activities, nor did the brilliant Confederate leader General Ewell reduce his mobility in the Shenandoah Valley on account of his. What a slap in the face for technocracy if all these modern prostheses, dressed in new shoes and pants, should languish behind the door except on state occasions! On thinking it all over, one finds it hard to escape the somewhat childish thought that a lot of waste motion could be saved simply by not blowing off peoples' arms and legs.

WHO RUNS MAY READ

THE *Lancet** comments philosophically on the replies made by twenty-five noted men and women when questioned on the subject, What Life Has Taught Me. Each pupil learned a different lesson in this universal schoolroom, for, as Dean Inge pointed out, "life teaches us what we are capable of learning."

Tolerance for others in order to do a good job oneself is the lesson gleaned by one of these receptive students of life; respect for the individual is the text that another has acquired, defined as a reluctance to inflict humiliation. Another finds logic in an immutable system of education that furnishes neither rewards nor punishments, but only consequences.

The editor of *Punch* is pleased at finding that his countrymen value their sense of humor above wisdom; an eminent divine, deriving lessons from illness, "urges the invalid to be patient with doctors, who are amazingly nice when tamed." Still another student at life's bench deplores certain indications that the dweller in cities seems often to have no interest that warms life.

"The bravest of these commentators," the *Lancet* concludes, "have given us the best reading."

*Annotations. Live to learn. *Lancet* 1:801, 1948.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

ROSMARIN — Ernest Rosmarin, M.D., of Boston, died on June 29. He was in his sixty-seventh year.

Dr. Rosmarin received his degree from Medizinische Fakultät der Universität, Vienna, in 1906.

A brother survives.

A HUNDRED YEARS AGO

A bright morning sun, on Wednesday last, gave promise of a pleasant meeting of the State Medical Society, which was fully realized. Nearly four hundred medical gentlemen dined together at a spacious hall on Hudson Street, instead of Faneuil Hall as previously announced. The entertainment was elegant, and satisfactory, we believe, to all present. Last year the income to the treasury was $1351.87 and the outgoes, $1038. About $200 are now on hand. The permanent fund of the Society, securely invested, in January next will amount to $11,000. A large and respectable committee, consisting of one from each medical district in the State, was raised to receive the delegates to the American Medical Association, who will assemble in Boston next year. A motion was made to authorize this committee to draw on the treasury for three hundred dollars. But this was voted down by an overwhelming majority, and a more lastingly mean act was never perpetrated by the Society. How is it possible to show the civilities of the Society, or exhibit even a semblance of sincere attention, without the means of doing so? The plea was raised in extenuation that the Society was poor. Yet there is the sum of eleven thousand dollars at interest, which if sunk in Lake Superior Copper Stock, would not have been considered by some of the members so great a loss as that occasioned by this parsimonious act. A spirit of false economy saved the money, while it disgraced the institution. Is it credible, as was said, that the Massachusetts Medical Society never exhibited more vigor, enterprise and soundness of constitution, than at the present moment? — Through the influence and at the expense of a lodge of Odd Fellows in Boston, the community have been furnished with a printed lecture by Charles E. Buckingham, M.D., on *Circumstances affecting individual and public health*. If the Odd Fellows pass their evening conclaves in listening to instruction like this, it will be at once conceded that they are persons of excellent taste and judgment, who contemplate the sufferings of the afflicted with a view to administering to their relief. The spirited author has an independent manner of giving his opinion, which reminds us of the tense style of his father. Dr. B. is no friend to physic, unless it is positively indicated. After the simple manner of the prophet, he would have all men wash and be clean — breathe fresh air and be well. On the subject of sewerage, which is of immense importance in cities and appreciated in Boston more than in most other cities, Dr. Buckingham is particularly emphatic. If the appropriate filth of sewers is suffered to run into the gutters of city streets, working its sluggish way, and exhaling, as it goes, a pestiferous stench, the

health of no one can remain safe, within the reach of its baneful influence. A new impulse has been given to the great inquiry — how shall apartments be supplied with pure air? No wonder that the victims of pulmonary consumption are multiplied to a fearful extent in New England, where close sleeping apartments, air-tight stoves, and almost air-tight rooms, are considered necessary to every-day comfort. A profound sense of the destruction of life from these and kindred sources, is happily manifesting itself by the public generally, as well as by influential individuals, so that the hope of a better sanitary constitution of society may reasonably be indulged. While thanking Dr. Buckingham for this strong argument in favor of reform, the lodge of Odd Fellows are entitled to the gratitude of all who are not odd, for their kind intentions in giving publicity to the discourse. — A kind of ring mania is existing in New England. It is enough that a penny paper advertisement declares that Dr. Cristy's Galvanic rings are a positive remedy for human maladies and many weak-minded people not only cover their fingers and neck, but their toes, with metallic hoops, which they imagine are charged with extraordinary medical powers. It is certain, however, that Dr. Cristy has no right to claim the practice of this nonsense, as his own discovery. It seems that in 1812 *galvanic beads* were all the rage in Boston, promising to accomplish nearly the same blessed results expected to flow from the more recently devised galvanic rings. — Another pamphlet on *The Ether Controversy* may soon be expected. Report says that Mr. Bowditch, one of the trustees of the Massachusetts General Hospital, is the author. The contest is likely to be perpetuated while the several claimants to the honor of having discovered the value of ether inhalation continue able to write and publish. — One of the anomalies of the present day, is the radicalism of practitioners of medicine. The community rings with the whims and caprices of those whose vocation is to interpret the language of nature, and medical schools are as much at variance with each other as individual practitioners. This creates confusion, engenders distrust in the public mind and lessens the confidence in those educated expressly to minister to human maladies. Indeed, there is an elevated class of citizens who countenance quackery in its thousand protean forms, because of the non-agreement of physicians, their radicalism and their want of confidence in the resources of medicine. — Extract of dandelion is becoming a new article of domestic manufacture. The dandelion possesses a medicinal value far above the estimate often placed upon it. As a detergent and aperient, and especially as a diuretic, it might well take the place of some other articles in use. — The approved modern treatment of acute gout has become well standardized. It should commence with a purgative, which may be a smart one if the patient is robust and plethoric — from ten to twenty grains of jalap, and from three to eight of calomel, followed in from two to five hours with a draught, consisting of equal parts of the infusion of rhubarb and senna, containing a drachm of sulphate of potass, and a scruple of that alkali. After this, a diaphoretic tisane, consisting of one or two drachms of ipecacuanha wine and four drachms of the solution of acetate of ammonia, in a pint and a half of weak tea, is to form the patient's drink. The patient is to eat little or nothing for twenty-four hours. At night, a full dose of Dover's powder may be given. This will relieve pain, secure sleep, promote diaphoresis — each an important object. On the third day, the use of colchicum may be begun. It is efficacious when given simply in doses of from twenty to sixty drops of the wine in four or six ounces of distilled water, along with from five to ten grains of the nitrate of potass. To this, two drachms of the compound spirit of juniper, and a half a drachm of the spirit of nitric ether may be added. Few persons can bear or will require a dose of sixty drops of colchicum wine oftener than twice in the twenty-four hours. Many cannot endure a half or third of that quantity. — Extracted from the *Boston Medical and Surgical Journal*, June–July, 1848.

R. F.

NOTICES

NEW YORK POST-GRADUATE HOSPITAL RESEARCH FELLOWSHIPS IN MEDICINE

Two appointments for research fellows in medicine for studies in the field of metabolic and degenerative diseases are available in the New York Post-Graduate Hospital immediately. Opportunities for ward studies, postgraduate courses and outpatient clinics are included. The salary is $3000 per annum.

Graduation from Grade A medical school and three years of approved hospital training in medicine and allied fields are required. Male and female applicants are acceptable. Applications should be addressed to Dr. John D. Currence, New York Post-Graduate Medical School and Hospital, 303 East 20th Street, New York 3, New York.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, September 14, at 8 p.m.

A scientific program will be presented by the Boston City Hospital Group.

PROGRAM

Symposium on Anesthesia for Thoracic Surgery.
Variations in Induction for Intubation. Dr. Sidney C. Wiggin.
Management of Positive Pressure. Dr. Peter Saunders.
As the Surgeon Sees Anesthesia for Thoracic Surgery. Dr. John W. Strieder.
Control of Cardiac Arrhythmia and Ventricular Fibrillation. Dr. Dwight E. Harken.

Physicians and medical students are invited to attend.

(*Notices concluded on page xiii*)